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APPLICATION NUMBER: *60/518,890*
FILING DATE: *November 10, 2003*
RELATED PCT APPLICATION NUMBER: *PCT/US04/37280*

Certified by

Jon W Dudas

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SUBSTITUTE for Provisional Application for Patent Cover Sheet PTO/SB/16 (08-03)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a **PROVISIONAL APPLICATION FOR PATENT** under **37 CFR 1.53 (c)**.

DOCKET NUMBER	21567PV

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22582 U.S.PTO 60/518890 111003

☒ *Additional inventors are being named on the 1 separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

SUBSTITUTED TRIAZOLES AS SODIUM CHANNEL BLOCKERS

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification — *Number of Pages* 89
☐ Drawing(s) — *Number of Sheets*
☐ Application Data Sheet. See 37 CFR 1.76
☐ CD(s), Number
☐ Other (specify)

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT *(check one)*

☐ A check or money order is enclosed to cover the filing fees

☒ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 13-2755

FILING FEE AMOUNT ($) $160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____ Date 11/07/2003

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NOTE: Mail to Mail Stop Provisional Application

EXPRESS MAIL CERTIFICATE

DATE OF DEPOSIT November 10, 2003

EXPRESS MAIL NO. EV321984317US

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MAILED BY _____ **DATE** November 10, 2003

In Duplicate

SUBSTITUTE for Provisional Application for Patent Cover Sheet PTO/SB/16 (08-03)
Approved for use through 07/31/2006. OMB 0651-0032
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PROVISIONAL APPLICATION COVER SHEET

Additional Page

DOCKET NUMBER	21567PV

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NUMBER 2 of 2

TITLE OF THE INVENTION

SUBSTITUTED TRIAZOLES AS SODIUM CHANNEL BLOCKERS

FIELD OF THE INVENTION

The present invention is directed to a series of substituted triazole compounds. In particular, this invention is directed to substituted triazoles that are sodium channel blockers useful for the treatment and prevention of chronic and neuropathic pain. The compounds of the present invention are also useful for the treatment of other conditions, including acute pain, inflammatory pain, visceral pain, migraine, headache pain, migraine headache, and disorders of the central nervous system (CNS) such as epilepsy, manic depression, bipolar disorder and diabetic neuropathy.

BACKGROUND OF THE INVENTION

Voltage-gated ion channels allow electrically excitable cells to generate and propagate action potentials and therefore are crucial for nerve and muscle function. Sodium channels play a special role by mediating rapid depolarization, which constitutes the rising phase of the action potential and in turn activates voltage-gated calcium and potassium channels. Voltage-gated sodium channels represent a multigene family. Nine sodium channel subtypes have been cloned and functionally expressed to date. [Clare, J. J., Tate, S. N., Nobbs, M. & Romanos, M. A. Voltage-gated sodium channels as therapeutic targets. *Drug Discovery Today* **5**, 506-520 (2000)]. They are differentially expressed throughout muscle and nerve tissues and show distinct biophysical properties. All voltage-gated sodium channels are characterized by a high degree of selectivity for sodium over other ions and by their voltage-dependent gating. [Catterall, W. A. Structure and function of voltage-gated sodium and calcium channels. *Current Opinion in Neurobiology* **1**, 5-13 (1991)]. At negative or hyperpolarized membrane potentials, sodium channels are closed. Following membrane depolarization, sodium channels open rapidly and then inactivate. Sodium channels only conduct currents in the open state and, once inactivated, have to return to the resting state, favored by membrane hyperpolarization, before they can reopen. Different sodium channel subtypes vary in the voltage range over which they activate and inactivate as well as in their activation and inactivation kinetics.

Sodium channels are the target of a diverse array of pharmacological agents, including neurotoxins, antiarrhythmics, anticonvulsants and local anesthetics. [Clare, J. J., Tate, S. N., Nobbs, M. & Romanos, M. A. Voltage-gated sodium channels as therapeutic targets. *Drug Discovery Today* **5**, 506-520 (2000)]. Several regions in the sodium channel secondary structure are involved in interactions with these blockers and most are highly conserved. Indeed, most sodium channel blockers known to date interact with similar potency with all channel subtypes. Nevertheless, it has been possible to produce sodium channel blockers with therapeutic selectivity and a sufficient therapeutic window for the treatment of epilepsy (e.g. lamotrigine, phenytoin and carbamazepine) and certain cardiac arrhythmias (e.g. lignocaine, tocainide and mexiletine).

It is well known that the voltage-gated Na^+ channels in nerves play a critical role in neuropathic pain. Injuries of the peripheral nervous system often result in neuropathic pain persisting long after the initial injury resolves. Examples of neuropathic pain include, but are not limited to, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, chronic lower back pain, phantom limb pain, pain resulting from cancer and chemotherapy, chronic pelvic pain, complex regional pain syndrome and related neuralgias. It has been shown in human patients as well as in animal models of neuropathic pain, that damage to primary afferent sensory neurons can lead to neuroma formation and spontaneous activity, as well as evoked activity in response to normally innocuous stimuli. [Carter, G.T. and B.S. Galer, *Advances in the management of neuropathic pain.* Physical Medicine and Rehabilitation Clinics of North America, 2001. **12**(2): p. 447-459]. The ectopic activity of normally silent sensory neurons is thought to contribute to the generation and maintenance of neuropathic pain. Neuropathic pain is generally assumed to be associated with an increase in sodium channel activity in the injured nerve. [Baker, M.D. and J.N. Wood, *Involvement of Na channels in pain pathways.* TRENDS in Pharmacological Sciences, 2001. **22**(1): p. 27-31.].

Indeed, in rat models of peripheral nerve injury, ectopic activity in the injured nerve corresponds to the behavioral signs of pain. In these models, intravenous application of the sodium channel blocker and local anesthetic lidocaine can suppress the ectopic activity and reverse the tactile allodynia at concentrations that do not affect general behavior and motor function. [Mao, J. and L.L. Chen, *Systemic lidocaine for neuropathic pain relief.* Pain, 2000. **87**: p. 7-17.]. These effective concentrations were similar to concentrations shown to be clinically

efficacious in humans. [Tanelian, D.L. and W.G. Brose, *Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers: lidocaine, carbamazepine and mexiletine.* Anesthesiology, 1991. **74**(5): p. 949-951.]. In a placebo-controlled study, continuous infusion of lidocaine casued reduced pain scores in patients with peripheral nerve injury, and in a separate study, intravenous lidocaine reduced pain intensity associated with postherpetic neuralgia (PHN). [Mao, J. and L.L. Chen, *Systemic lidocaine for neuropathic pain relief.* Pain, 2000. **87**: p. 7-17. Anger, T., et al., *Medicinal chemistry of neuronal voltage-gated sodium channel blockers.* Journal of Medicinal Chemistry, 2001. **44**(2): p. 115-137.]. Lidoderm®, lidocaine applied in the form of a dermal patch, is currently the only FDA approved treatment for PHN. [Devers, A. and B.S. Galer, *Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study.* Clinical Journal of Pain, 2000. **16**(3): p. 205-208.].

In addition to neuropathic pain, sodium channel blockers have clinical uses in the treatment of epilepsy and cardiac arrhythmias. Recent evidence from animal models suggests that sodium channel blockers may also be useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and in patients with multiple sclerosis (MS). [Clare, J. J. *et. al.* And Anger, T. *et. al.*].

International Patent Publication WO 00/57877 describes aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles, and pyrroles and their uses as sodium channel blockers. International Patent Publication WO 01/68612 describes aryl substituted pyridines, pyrimidines, pyrazines and triazines and their uses as sodium channel blockers. International Patent Publication WO 99/32462 describes triazine compounds for the treatment for CNS disorders. However, there remains a need for novel compounds and compositions that therapeutically block neuronal sodium channels with less side effects and higher potency than currently known compounds.

SUMMARY OF THE INVENTION

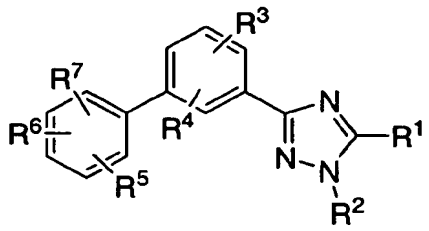
The present invention is directed to substituted triazole compounds which are sodium channel blockers useful for the treatment and prevention of chronic and neuropathic pain. The compounds of the present invention are also useful for the treatment and prevention of other conditions, including disorders of the CNS such as epilepsy, manic depression and bipolar disorder. This invention also provides pharmaceutical compositions comprising a compound of

the present invention, either alone, or in combination with one or more therapeutically active compounds, and a pharmaceutically acceptable carrier.

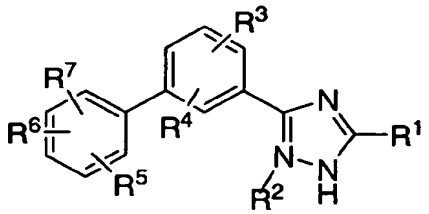
This invention further comprises methods for the treatment and prevention of acute pain, visceral pain, migraine, headache pain, migraine headache, inflammatory pain, and disorders of the CNS including, but not limited to, epilepsy, manic depression and bipolar disorder comprising administering the comounds and pharmaceutical compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises compounds represented by Formula (I) or (II):



(I)



(II)

or pharmaceutically acceptable salts thereof, wherein

R^1 is

(a) H,

(b) C_1-C_6-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, any of which is optionally substituted with one or more of the following substituents: NR^aR^b, COOH, $CONR^aR^b$, or

(c) -C(=O)R^a, $COOR^a$, $CONR^aR^b$;

R^a is

(a) H,
(b) C_1-C_6-alkyl, optionally substituted with one or more of halogen or CF_3, or
(c) CF_3;

R^b is

(a) H, or
(b) C_1-C_6-alkyl, optionally substituted with one or more of halogen or CF_3, or
(c) CF_3;

R^2 is H or C_{1-4} alkyl;

R^3 and R^4 each independently is

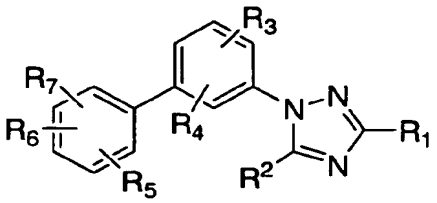
(a) H,
(b) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl,
(c) halogen, or
(d) –C_1-C_6 alkyl, optionally substituted with one or more of halogen or CF_3; and

R^5, R^6 and R^7each independently is

(a) H,
(b) -O- C_1-C_6-alkyl, -O- C_1-C_6-alkenyl, -O- C_1-C_6-alkynyl, any of which is optionally substituted with one or more of halogen or CF_3,
(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl,
(d) -O-phenyl, or -O-C_1-C_4-alkyl-phenyl, wherein phenyl is optionally substituted with 1-3 substituents selected from i) halogen, ii) -CN, iii) $-NO_2$, iv) CF_3, v) $-OR^a$, vi) $-NR^aR^b$, vii) –C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-CO-$N(R^a)(R^b)$, ix) and x) -C_{1-10} alkyl,wherein one or more of the alkyl carbons can be replaced by a –NR^a, C(O)-O-, or -$N(R^a)$-C(O)-$N(R^a)$-, or

(e) halogen, -OR^a, or phenyl wherein phenyl is optionally substituted with 1-3 substituents selected from i) halogen, ii) -CN, iii) $-NO_2$, iv) CF_3, v) pyrazolyl, vi) -OR^a, vii) -NR^aR^b, viii) -C_{0-4}alkyl-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-$N(R^a)(R^b)$, and x) $-C_{1-10}$alkyl, wherein one or more of the alkyl carbons can be replaced by a $-NR^a$, C(O)-O-, or -$N(R^a)$-C(O)-$N(R^a)$-.

The present invention further comprises compounds described by Formula III:



(III)

or pharmaceutical salts thereof, wherein

$R^1 - R^7$ each is as defined above.

In a first aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H and is attached at the ortho position.

In one embodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted phenyl.

In a second emobodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted -O- C_1-C_6-alkyl.

In a third embodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is $-O-C_1-C_4$-alkyl-phenyl, wherein phenyl is optionally substituted.

In another embodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^6 is halogen.

In an additional embodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 is halogen.

In a further embodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 and R^4 are halogen.

In a still further embodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4 and R^6 are halogen.

In yet another embodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 is -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl.

In a yet still further embodiment of this first aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted -O- C_1-C_6-alkenyl.

In a second aspect, the present invention provides a compound described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H and is attached at the ortho position.

In one embodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted phenyl.

In a second embodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is –O-C_1-C_4-alkyl-phenyl, wherein phenyl is optionally substituted.

In a third embodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted –O-C_1-C_6-alkenyl.

In a fourth emobodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted -O- C_1-C_6-alkyl.

In another embodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^6 is halogen.

In an additional embodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 is halogen.

In a further embodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 and R^4 are halogen.

In a still further embodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4 and R^6 are halogen.

In yet another embodiment of this second aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 is -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl.

In a third aspect, the present invention provides a compound described by the chemical Formula (III), or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H and is attached at the ortho position.

In one embodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted phenyl.

In a second emobodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted -O- C_1-C_6-alkyl.

In a third embodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is –O-C_1-C_4-alkyl-phenyl, wherein phenyl is optionally substituted.

In a fourth embodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted –O-C_1-C_6-alkenyl.

In another embodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 is halogen.

In a further embodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^6 is halogen.

In a still further embodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 and R^4 are halogen.

In a yet still further embodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4 and R^6 are halogen.

In yet another embodiment of this third aspect, the present invention provides a compound, or a pharmaceutically acceptable salt thereof, wherein

R^3 is -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, and alkynyl means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, and heptyl. "Alkenyl," "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The terms "C_{0-4}alkyl" and "C_0-C_4-alkyl" include alkyls containing 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

The term "amine," unless specifically stated otherwise, includes primary, secondary and tertiary amines substituted with C_{0-6}alkyl.

The term "carbonyl," unless specifically stated otherwise, includes a C_{0-6}alkyl substituent group when the carbonyl is terminal.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted phenyl could represent a pentafluorophenyl or a phenyl ring. Further, optionally substituted multiple moieties such as, for example, alkyl-phenyl are intended to mean that the alkyl and the phenyl groups are optionally substituted. If only one of the multiple moieties is optionally substituted then it will be

specifically recited such as "an -O–C_1-C_4-alkyl-phenyl, wherein phenyl is optionally substituted with halogen."

Compounds described herein may contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers unless specifically stated otherwise. When the indicated site has only a single bond, the presence of the required hydrogens is understood. When the site is a double bond, then cis/trans isomers are formed and are encompassed by this invention.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereoisomers and optical isomers. The present invention includes all such possible diastereoisomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above chemical Formulas are shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of the chemical Formulas and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-

ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and tromethamine.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds of this invention which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985. Metabolites of these compounds include active species produced upon introduction of compounds of this invention into the biological milieu.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I, II or III (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. Such additional therapeutic agents can include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, and xiv) neurontin (gabapentin). The

instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The present compounds and compositions are useful for the treatment and prevention of chronic, visceral, inflammatory and neuropathic pain syndromes. The present compounds and compositions are also useful for the treatment and prevention of other conditions, including acute pain, migraine, headache pain, and migraine headache. They are useful for the treatment and prevention of pain resulting from traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, and diabetic neuropathy. The present compounds and compositions are also useful for the treatment and prevention of chronic lower back pain, phantom limb pain, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgias, and pain associated with cancer, chemotherapy, HIV and HIV treatment-induced neuropathy. Compounds of this invention may also be utilized as local anesthetics. Compounds of this invention are useful for the treatment and prevention of irritable bowel syndrome and related disorders, as well as Crohns disease.

The instant compounds have clinical uses for the treatment and prevention of epilepsy and partial and generalized tonic seizures. They are also useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and for treating multiple sclerosis. The present compounds are useful for the treatment and prevention of bipolar disorder and tachy-arrhythmias.

It is understood that compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions, as well as to prevent other conditions associated with sodium channel activity.

Creams, ointments, jellies, solutions, or suspensions containing the instant compounds can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of inflammatory and neuropathic pain, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammatory pain may be effectively treated by the administration of from about 0.01mg to about 75mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Neuropathic pain may be effectively treated by the administration of from about 0.01mg to about 125mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 5.5g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such patient-related factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, II and III or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms

set out above, the compounds represented by Formula I, II and III or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention can include a pharmaceutically acceptable carrier and compounds or pharmaceutically acceptable salts of Formula I, II and/or III. The compounds of Formula I, II and III, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent.

Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, and dusting powder. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I, II or III, or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the

art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, and preservatives (including anti-oxidants). Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, II or III, or a pharmaceutically acceptable salt thereof, can also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to block sodium channels. Accordingly, an aspect of the invention is the treatment in mammals of maladies that are amenable to amelioration through blockage of neuronal sodium channels, including, for example, acute pain, chronic pain, visceral pain, inflammatory pain, and neuropathic pain by administering an effective amount of a compound of this invention. The term "mammals" includes humans, as well as other animals, such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than humans refers to the treatment of clinical conditions in non-human mammals that correlate to the above-recited conditions.

Further, as described above, the instant compounds can be utilized in combination with one or more therapeutically active compounds. In particular, the inventive compounds can be advantageously used in combination with i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists iv) sodium channel antagonists, v) N-methyl-D-aspartate (NMDA) receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) neurokinin receptor 1 (NK1) antagonists, viii) non-steroidal anti-inflammatory drugs (NSAID), ix) selective serotonin reuptake inhibitors (SSRI) and/or selective serotonin and norepinephrine reuptake inhibitors (SSNRI), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, and xiv) neurontin (gabapentin).

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless specifically stated otherwise.

Ac	Acetyl
AIBN	2,2'-azobis(isobutyronitrile)
BINAP	1,1'-bi-2-naphthol
Bn	Benzyl
CAMP	cyclic adenosine-3',5'-monophosphate
DAST	(diethylamino)sulfur trifluoride
DEAD	diethyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
Dppf	1,1'-bis(diphenylphosphino)-ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et_3N	Triethylamine
GST	glutathione transferase
HMDS	Hexamethyldisilazide
LDA	lithium diisopropylamide
m-CPBA	metachloroperbenzoic acid
MMPP	monoperoxyphthalic acid
MPPM	monoperoxyphthalic acid, magnesium salt $6H_2O$
Ms	methanesulfonyl = mesyl = SO_2Me
Ms0	methanesulfonate = mesylate
NBS	N-bromo succinimide
NSAID	non-steroidal anti-inflammatory drug
o-Tol	ortho-tolyl
OXONE®	$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$
PCC	pyridinium chlorochromate
$Pd_2(dba)_3$	Bis(dibenzylideneacetone) palladium(0)

PDC	pyridinium dichromate
PDE	Phosphodiesterase
Ph	Phenyl
Phe	Benzenediyl
PMB	para-methoxybenzyl
Pye	Pyridinediyl
r.t.	room temperature
Rac.	Racemic
SAM	aminosulfonyl or sulfonamide or SO_2NH_2
SEM	2-(trimethylsilyl)ethoxymethoxy
SPA	scintillation proximity assay
TBAF	tetra-n-butylammonium fluoride
Th	2- or 3-thienyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	Tetrahydrofuran
Thi	Thiophenediyl
TLC	thin layer chromatography
TMS-CN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
Tz	1H (or 2H)-tetrazol-5-yl
XANTPHOS	4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene
C_3H_5	Allyl

ALKYL GROUP ABBREVIATIONS

Me	=	Methyl
Et	=	ethyl
n-Pr	=	normal propyl

i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

The following *in vitro* and *in vivo* assays were used in assessing the biological activity of the instant compounds.

Compound Evaluation (*in vitro* assay):

The identification of inhibitors of the sodium channel is based on the ability of sodium channels to cause cell depolarization when sodium ions permeate through agonist-modified channels. In the absence of inhibitors, exposure of an agonist-modified channel to sodium ions will cause cell depolarization. Sodium channel inhibitors will prevent cell depolarization caused by sodium ion movement through agonist-modified sodium channels. Changes in membrane potential can be determined with voltage-sensitive fluorescence resonance energy transfer (FRET) dye pairs that use two components, a donor coumarin (CC_2DMPE) and an acceptor oxanol ($DiSBAC_2(3)$). Oxanol is a lipophilic anion and distributes across the membrane according to membrane potential. In the presence of a sodium channel agonist, but in the absence of sodium, the inside of the cell is negative with respect to the outside, oxanol is accumulated at the outer leaflet of the membrane and excitation of coumarin will cause FRET to occur. Addition of sodium will cause membrane depolarization leading to redistribution of oxanol to the inside of the cell, and, as a consequence, to a decrease in FRET. Thus, the ratio change (donor/acceptor) increases after membrane depolarization. In the presence of a sodium channel inhibitor, cell depolarization will not occur, and therefore the distribution of oxanol and FRET will remain unchanged.

Cells stably transfected with the PN1 sodium channel (HEK-PN1) were grown in polylysine-coated 96-well plates at a density of ca. 140,000 cells/well. The media was aspirated, and the cells were washed with PBS buffer, and incubated with 100µL of 10µM CC_2-DMPE in 0.02% pluronic acid. After incubation at 25°C for 45min, media was removed and cells were washed 2x with buffer. Cells were incubated with 100µL of $DiSBAC_2(3)$ in TMA buffer containing 20µM veratridine, 20nM brevetoxin-3, and test sample. After incubation at 25°C for 45min in the dark, plates were placed in the VIPR instrument, and the fluorescence emission of both CC_2-DMPE and $DiSBAC_2(3)$ recorded for 10s. At this point, 100µL of saline buffer was added to the wells to determine the extent of sodium-dependent cell depolarization, and the fluorescence emission of both dyes recorded for an additional 20s. The ratio CC_2-DMPE/$DiSBAC_2(3)$, before addition of saline buffer equals 1. In the absence of inhibitors, the ratio after addition of saline buffer is > 1.5. When the sodium channel has been completely inhibited by either a known standard or test compound, this ratio remains at 1. It is possible, therefore, to titrate the activity of a sodium channel inhibitor by monitoring the concentration-dependent change in fluorescence ratio.

Electrophysiological Assays (*In Vitro* assays):

Cell preparation: A HEK-293 cell line stably expressing the PN1 sodium channel subtype was established in-house. The cells were cultured in MEM growth media (Gibco) with 0.5mg/mL G418, 50 units/mL Pen/Strep and 1mL heat-inactivated fetal bovine serum at 37°C and 10% CO_2. For electrophysiological recordings, cells were plated on 35mm dishes coated with poly-D-lysine.

Whole-cell recordings: HEK-293 cells stably expressing the PN1 sodium channel subtype were examined by whole cell voltage clamp (Hamill et. al. Pfluegers Archives 391:85-100 (1981)) using an EPC-9 amplifier and Pulse software (HEKA Electronics, Lamprecht, Germany). Experiments were performed at room temperature. Electrodes were fire-polished to resistances of 2-4 MΩ. Voltage errors were minimized by series resistance compensation, and the capacitance artefact was canceled using the EPC-9's built-in circuitry. Data were acquired at 50 kHz and filtered at 7-10 kHz. The bath solution consisted of 40 mM NaCl, 120 mM NMDG Cl, 1 mM KCl, 2.7 mM $CaCl_2$, 0.5 mM $MgCl_2$, 10 mM NMDG HEPES, pH 7.4, and the internal

(pipet) solution contained 110 mM Cs-methanesulfonate, 5 mM NaCl, 20mM CsCl, 10mM CsF, 10 mM BAPTA (tetra Cs salt), 10 mM Cs HEPES, pH 7.4.

The following protocols were used to estimate the steady-state affinity of compounds for the resting and inactivated state of the channel (K_r and K_i, respectively):

1) 8ms test-pulses to depolarizing voltages from –60mV to +50mV from a holding potential of –90mV were used to construct current-voltage relationships (IV-curves). A voltage near the peak of the IV-curve (typically –10 or 0 mV) was used as the test-pulse voltage throughout the remainder of the experiment.

2) Steady-state inactivation (availability) curves were constructed by measuring the current activated during an 8ms test-pulse following 10s conditioning pulses to potentials ranging from –120mV to –10mV.

3) Compounds were applied at a holding potential at which 20-50% of the channels was inactivated and sodium channel blockage was monitored during 8ms test pulses at 2s intervals.

4) After the compounds equilibrated, the voltage-dependence of steady-state inactivation in the presence of compound was determined according to protocol 2) above. Compounds that block the resting state of the channel decrease the current elicited during test-pulses from all holding potentials, whereas compounds that primarily block the inactivated state shift the mid-point of the steady-state inactivation curve. The maximum current at negative holding potentials (I_{max}) and the difference in the mid-points of the steady-state inactivation curves (ΔV) in control and in the presence of a compound were used to calculate K_r and K_i using the following equations:

$$K_r = \frac{[Drug] * I_{Max,Drug}}{I_{Max,Control} - I_{Max,Drug}}$$

$$K_i = \frac{[Drug]}{\left(1 + \frac{[Drug]}{K_r}\right) * e^{\frac{-\Delta V}{k}} - 1}$$

In cases where the compound did not affect the resting state, K_i was calculated using the following equation:

$$K_i = \frac{[Drug]}{e^{\frac{-\Delta V}{k}} - 1}$$

Rat Formalin Paw test (*in vivo* assay):

Compounds were assessed for their ability to inhibit the behavioral response evoked by a 50µL injection of formalin (5%). A metal band was affixed to the left hind paw of male Sprague-Dawley rats (Charles River, 200-250g) and each rat was conditioned to the band for 60min within a plastic cylinder (15cm diameter). Rats were dosed with either vehicle or a test compound either before (local) or after (systemic) formalin challenge. For local administration, compounds were prepared in a 1:4:5 vehicle of ethanol, PEG400 and saline (EPEGS) and injected subcutaneously into the dorsal surface of the left hind paw 5min prior to formalin. For systemic administration, compounds were prepared in either a EPEGS vehicle or a Tween80 (10%)/sterile water (90%) vehicle and were injected i.v. (via the lateral tail vein 15min after formalin) or p.o. (60min before formalin). The number of flinches was counted continuously for 60min using an automated nociception analyzer (UCSD Anesthesiology Research, San Diego, CA). Statistical significance was determined by comparing the total flinches detected in the early (0-10min) and late (11-60min) phase with an unpaired t-test.

***In vivo* assay using Rat CFA model:**

Unilateral inflammation was induced with a 0.2 ml injection of complete Freund's adjuvant (CFA: Mycobacterium tuberculosis, Sigma; suspended in an oil/saline (1:1) emulsion; 0.5mg Mycobacterium/mL) in the plantar surface of the left hindpaw. This dose of CFA produced significant hind paw swelling but the animals exhibited normal grooming behavior and weight gain over the course of the experiment. Mechanical hyperalgesia was assessed 3 days after tissue injury using a Randall-Selitto test. Repeated Measures ANOVA, followed by Dunnett's Post Hoc test.

SNL: Mechanical Allodynia (*in vivo* assay):

Tactile allodynia was assessed with calibrated von Frey filaments using an up-down paradigm before and two weeks following nerve injury. Animals were placed in plastic

cages with a wire mesh floor and allowed to acclimate for 15min before each test session. To determine the 50% response threshold, the von Frey filaments (over a range of intensities from 0.4 to 28.8g) were applied to the mid-plantar surface for 8s, or until a withdrawal response occurred. Following a positive response, an incrementally weaker stimulus was tested. If there was no response to a stimulus, then an incrementally stronger stimulus was presented. After the initial threshold crossing, this procedure was repeated for four stimulus presentations per animal per test session. Mechanical sensitivity was assessed 1 and 2 hr post oral administration of the test compound.

The compounds described in this invention displayed sodium channel blocking activity of from about <0.1μM to about <50μM in the *in vitro* assays described above. It is advantageous that the compounds display sodium channel blocking activity of <5μM in the *in vitro* assays. It is more advantageous that the compounds display sodium channel blocking activity of <1μM in the *in vitro* assays. It is even more advantageous that the compounds display sodium channel blocking activity of <0.5μM in the *in vitro* assays. It is still more advantageous that the compounds display sodium channel blocking activity of <0.1μM in the *in vitro* assays.

The present compounds can be prepared according to the general schemes provided below as well as the procedures provided in the Examples. The following schemes and Examples further describe, but do not limit, the scope of the invention.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions: All operations were carried out at room or ambient temperature; that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz,

400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

Methods of Synthesis

Compounds of the present invention can be prepared according to the Schemes provided below as well as the procedures provided in the Reference Examples and Examples. The substituents are the same as in the above Formulas except where defined otherwise or otherwise apparent to the ordinary skilled artisan.

The novel compounds of the present invention can be readily synthesized using techniques known to those skilled in the art, such as those described, for example, in Advanced Organic Chemistry, March, 4th Ed., John Wiley and Sons, New York, NY, 1992 ; Advanced Organic Chemistry, Carey and Sundberg, Vol. A and B, 3rd Ed., Plenum Press, Inc., New York, NY, 1990; Protective groups in Organic Synthesis, Green and Wuts, 2nd Ed., John Wiley and Sons, New York, NY, 1991; Comprehensive Organic Transformations, Larock, VCH Publishers, Inc., New York, NY, 1988; Handbook of Heterocyclic Chemistry, Katritzky and Pozharskii, 2nd Ed., Pergamon, New York, NY, 2000 and references cited therein. The starting materials for the present compounds may be prepared using standard synthetic transformations of chemical precursors that are readily available from commercial sources, including Aldrich Chemical Co. (Milwaukee, WI); Sigma Chemical Co. (St. Louis, MO); Lancaster Synthesis (Windham, N.H.); Ryan Scientific (Columbia, S. C.); Maybridge (Cornwall, UK); Matrix Scientific (Columbia, S. C.); Arcos, (Pittsburgh, PA) and Trans World Chemicals (Rockville, MD).

The procedures described herein for synthesizing the compounds may include one or more steps of protecting group manipulations and of purification, such as, recrystallization, distillation, column chromatography, flash chromatography, thin-layer chromatography (TLC), radial chromatography and high-pressure chromatography (HPLC). The products can be characterized using various techniques well known in the chemical arts, including proton and carbon-13 nuclear magnetic resonance (^{1}H and ^{13}C NMR), infrared and ultraviolet spectroscopy (IR and UV), X-ray crystallography, elemental analysis and HPLC and mass spectrometry (LC-

MS). Methods of protecting group manipulation, purification, structure identification and quantification are well known to one skilled in the art of chemical synthesis.

Appropriate solvents are those which will at least partially dissolve one or all of the reactants and will not adversely interact with either the reactants or the product. Suitable solvents are aromatic hydrocarbons (e.g, toluene, xylenes), halogenated solvents (e.g, methylene chloride, chloroform, carbontetrachloride, chlorobenzenes), ethers (e.g, diethyl ether, diisopropylether, tert-butyl methyl ether, diglyme, tetrahydrofuran, dioxane, anisole), nitriles (e.g, acetonitrile, propionitrile), ketones (e.g, 2-butanone, dithyl ketone, tert-butyl methyl ketone), alcohols (e.g, methanol, ethanol, n-propanol, iso-propanol, n-butanol, t-butanol), dimethyl formamide (DMF), dimethylsulfoxide (DMSO) and water. Mixtures of two or more solvents can also be used. Suitable bases are, generally, alkali metal hydroxides, alkaline earth metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, and calcium hydroxide; alkali metal hydrides and alkaline earth metal hydrides such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal amides such as lithium amide, sodium amide and potassium amide; alkali metal carbonates and alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, Cesium carbonate, sodium hydrogen carbonate, and cesium hydrogen carbonate; alkali metal alkoxides and alkaline earth metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and magnesium ethoxide; alkali metal alkyls such as methyllithium, n-butyllithium, sec-butyllithium, t-bultyllithium, phenyllithium, alkyl magnaesium halides, organic bases such as trimethylamine, triethylamine, triisopropylamine, N,N-diisopropylethylamine, piperidine, N-methyl piperidine, morpholine, N-methyl morpholine, pyridine, collidines, lutidines, and 4-dimethylaminopyridine; and bicyclic amines such as DBU and DABCO.

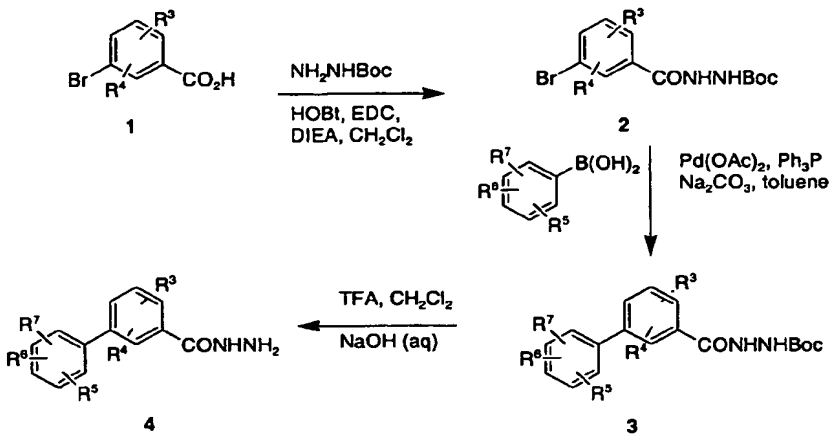
As described previously, in preparing the compositions for oral dosage form, any of the usual pharmaceutical media can be employed. For example, in the case of oral liquid preparations such as suspensions, elixirs and solutions, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used; or in the case of oral solid preparations such as powders, capsules and tablets, carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents,

and the like may be included. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. In addition to the common dosage forms set out above, controlled release means and/or delivery devices may also be used in administering the instant compounds and compositions.

It is understood that the functional groups present in compounds described in the Schemes below can be further manipulated, when appropriate, using the standard functional group transformation techniques available to those skilled in the art, to provide desired compounds described in this invention.

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

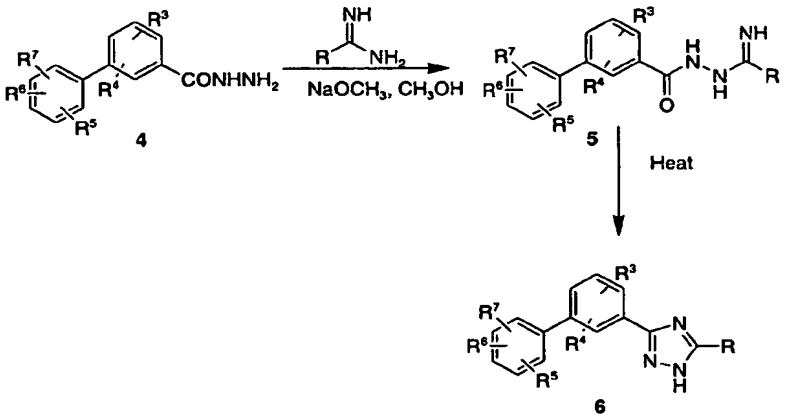
SCHEME 1



In accordance with Scheme 1, 3-bromobenzoic acid **1** is coupled with t-butyl carbazate by activation with HOBt (hydroxybenzotriazole) in the presence of a suitable carbodiimide such as EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) and diisopropylethylamine (DIEA) in dichloromethane or THF to give the protected hydrazide **2**. There are numerous other suitable methods to activate carboxylic acids for coupling formation (see March J., Advanced Organic Chemistry, 5th ed., John Wiley & Sons, New York, pp. 506-512 (2001)). Compound **2** can be converted to a variety of unsymmetrical biphenyl intermediates **3** by means of a variety of coupling reactions. One type is the Suzuki reaction wherein bromo, iodo, or triflate compound **2** is reacted with an aryl boronic acid in the presence of a palladium catalyst such as palladium acetate with triphenyl phosphine and aqueous sodium carbonate in a solvent such as toluene and a co-solvent such as n-propanol. (see Suzuki et. al., *Chem. Rev.*, 95, 2457, 1995). A variety of aryl boronic acids are commercially available or can be prepared conveniently from the corresponding aryl bromide or iodide by converting it to an organolithium derivative [Baldwin, J. E. et al., *Tetrahedron Lett.* 39, 707-710 (1998)], or a Grignard reagent followed by treatment with trialkylborate [Li, J. J. et al, *J. Med. Chem*, 38: 4570-4578(1995) and Piettre, S. R. et al. *J. Med Chem.* 40, 4208-4221 (1997)]. Aryl boronates

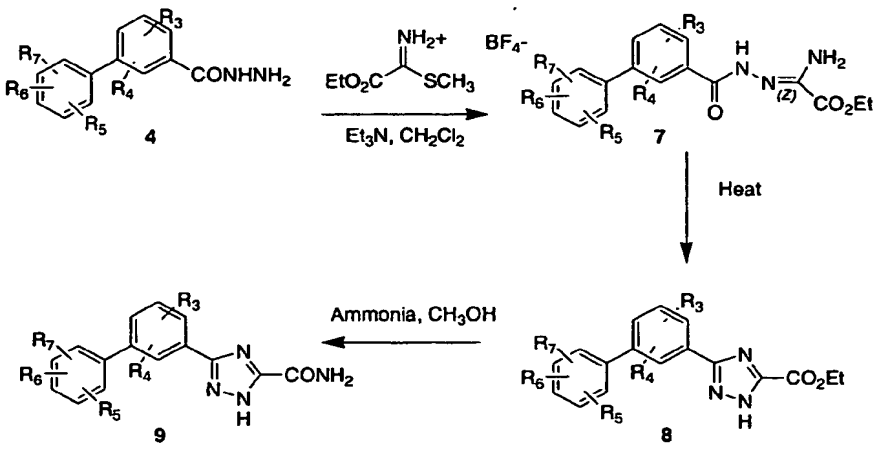
can also be used as an alternative to aryl boronic acids in these Pd-catalyzed coupling reactions [Giroux, A. et. al., *Tetrahedron Lett.*, 38, 3841(1997)]. The boronates can be easily prepared from the aryl bromides, iodides and trifluoromethane sulfonates using the method described by [Murata, M. et. al., *J. Org. Chem.* 65: 164-168 (2000)]. The Boc protecting group of compound 3 is removed by standard conditions - trifluoroacetic acid in dichloromethane - to give the TFA salt of hydrazide **4** which can be desalted with aqueous NaOH solution.

SCHEME 2



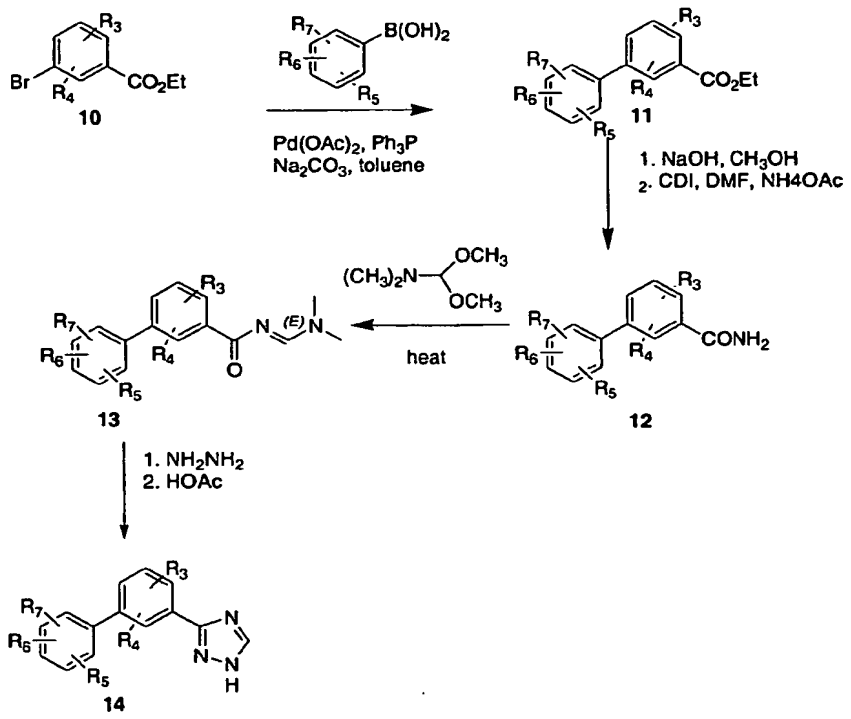
In Scheme 2, a method for preparing 5-biphenyl-3-substituted 1, 2, 4-triazole derivatives is described (Francis et. al., *Tetrahedron Lett.*, 28(43), 5133-5136, 1987). Reaction of hydrazide **4** with a substituted amidine with a base such as sodium methoxide in methanol gives intermediate **5** which, on heating neat (no co-solvent), gives triazole **6**.

SCHEME 3



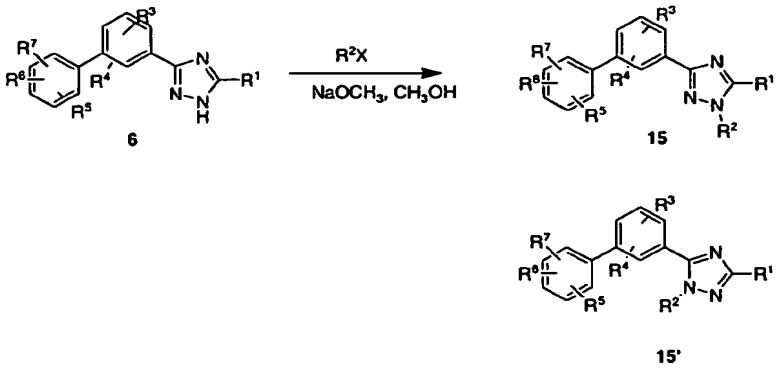
In Scheme 3, a method is described for preparing 5-biphenyl-3-substituted-1, 2, 4-triazole derivatives wherein the substitution can be esters, acids, amides, etc. (Catarzi et. al., *J. Med. Chem.*, 38, 2196-2201, (1995)). Reaction of hydrazide **4** with carbethoxy-S-methyl-thioformimidium tetrafluoroborate and triethylamine in dichloromethane gives oxamidrazonate **7** which is cyclized to triazole ester **8**. The reagent carbethoxy-S-methyl-thioformimidium tetrafluoroborate is prepared by reaction of ethyl-2-thiooxamate with trimethyl oxonium tetrafluoroborate (see Catarzi *et. al.* above) in dichloromethane. Ester **8** can be converted to a variety of amides simply by heating it with the corresponding amine, in this case ammonia, in a solvent such as methanol.

SCHEME 4



In Scheme 4, a method is described for preparing an unsubstituted 3-triazole ring system (Lin et.al, *J.Org. Chem.*, 44(23), 4160-4165, 1979). Ethyl-3-bromobenzoate **10** is reacted with an aryl boronic acid as described in Scheme 1 to give biphenylester **11.** The ester **11** provides a preformed biphenyl intermediate that can be further elaborated to compound **4** and related derivatives as described in earlier Schemes 1-3. In this Scheme 4, ester **11** is converted to amide **12** under standard conditions. Specifically, ester **11** is hydrolyzed to the corresponding acid which is then activated with carbonyldiimidazole (CDI) in DMF, followed by the addition of ammonia in the form of ammonium acetate to give amide **12.** Amide **12** in dimethylformamide dimethylacetal is heated to give intermediate **13** which, when heated with hydrazine in acetic acid, gives triazole **14.**

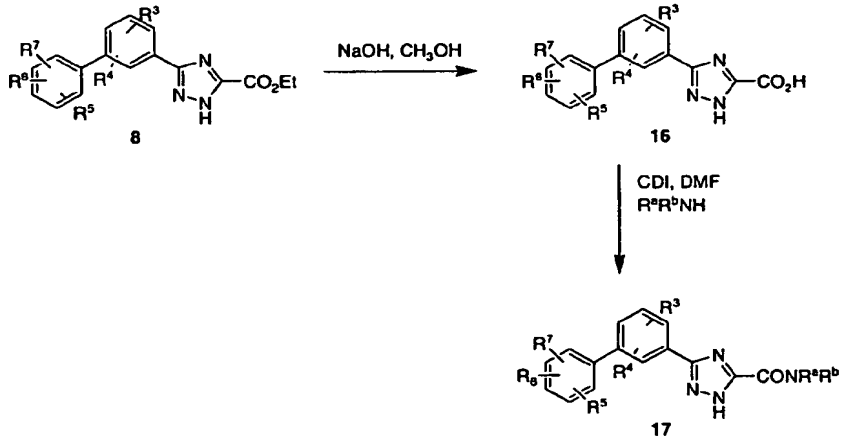
SCHEME 5



6 15 15'

In Scheme 5, alkylation of triazole **6** by using a base such as sodium methoxide in a solvent such as methanol with an akylhalide or triflate gives a mixture of tautomeric products **15** and **15'**.

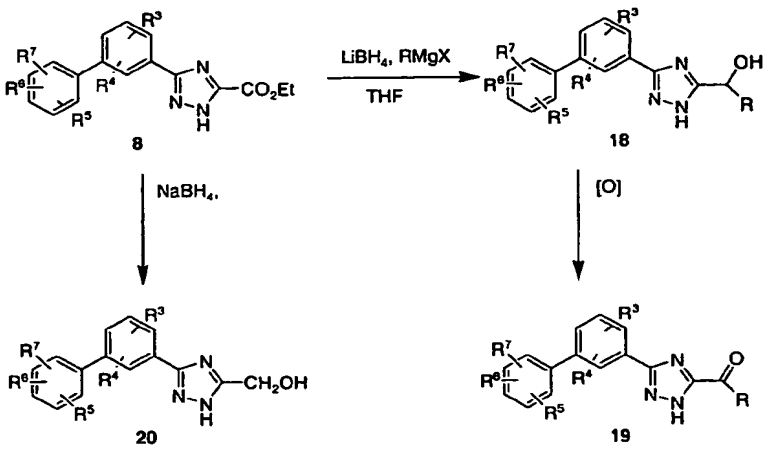
SCHEME 6



8 16 17

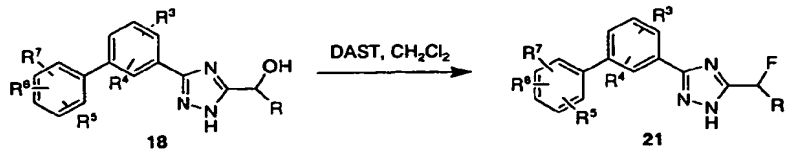
In Scheme 6, triazole ester **8** can be hydrolyzed to acid **16** under standard conditions (sodium hydroxide, methanol). Acid **16** can be converted to amide **17** under a variety of conditions described in Scheme 1. In this variation, activation of acid **16** with carbonyldiimidazole (CDI) in dimethylformamide (DMF) followed by addition of an amine gives amide **17**.

SCHEME 7



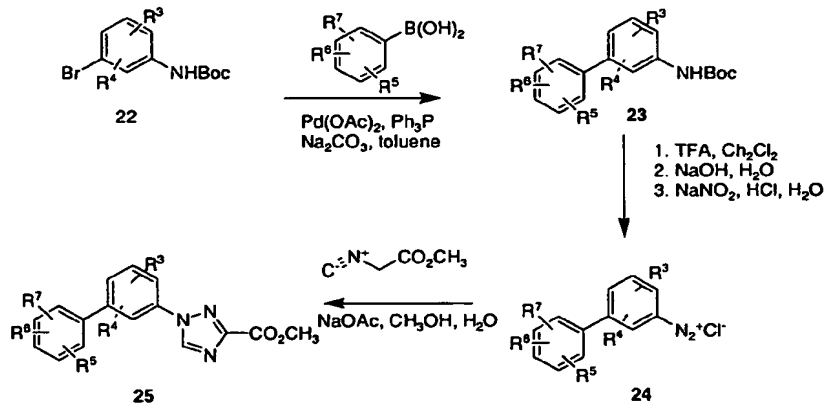
In Scheme 7, triazole ester **8** can be converted to a secondary alcohol **18** as the major product by reaction with a mixture of lithium borohydride and a Grignard reagent in an aprotic solvent such as THF. Alternatively, ester **8** can be reduced to primary alcohol **20** by any of several reducing agents, which include lithium aluminum hydride (LAH), diisobutylaluminum hydride (DIBAL-H) and sodium borohydride ($NaBH_4$). Either alcohol **18** or **20** can be further derivatized by any number of methods. In one example, alcohol **18** can be oxidized to the ketone **19** by a variety of oxidizing reagents which include chromium-based reagents, and Swern type reagents (DMSO and oxalyl chloride).

SCHEME 8



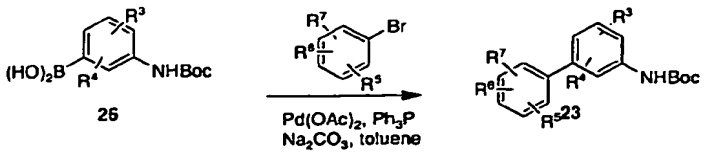
The alcohol **18** also can be converted to fluoride derivative **21** by reaction with diethylaminosulfurtrifluoride (DAST) in dichlormethane at reduced temperatures, as described in Scheme 8.

SCHEME 9



In accordance with Scheme 9, bromoaniline **22,** wherein the amino group is protected with a Boc group, and an arylboronic acid is converted to a variety of unsymmetrical biphenyl intermediates **23** as described in Scheme 1. The Boc protecting group of compound **23** is removed as described previously and converted to its diazonium salt **24** by standard reaction with sodium nitrite and HCl in water. Addition of compound **24** to a mixture of methylisocyanoacetate and sodium acetate in methanol and water gave the triazole ester **25**. The key intermediate **25** can be then converted to a variety of useful derivatives using the methods described in Schemes 1-7.

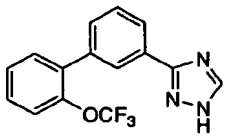
SCHEME 10



In Scheme 10, which is a variation to the protocols described in Schemes 1, 4 and 9 above, the Boc-protected anline **26** containing a boronic acid group or boronate ester and an aryl bromide, iodide or triflate is converted to a variety of unsymmetrical biphenyl intermediates **23** as described in Scheme 1.

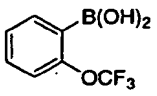
The following Reference Examples provide methods for preparing certain compounds of the invention:

REFERENCE EXAMPLE 1



3-[3-(2-Trifluoromethoxyphenyl)-phenyl]-1,2,4-triazole

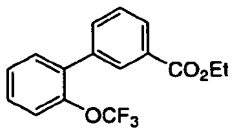
Step A: 2-Trifluoromethoxyphenylboronic acid



To a stirred solution of 2 g (9.5 mmol) of 1-bromo-2-trifluoromethoxy benzene in 28 mL of tetrahydrofuran (THF) at – 78°C, was carefully added 5.9 mL of a 1.7 M solution of t-butyl lithium in hexanes (9.5 mmol). This reaction mixture was stirred at -78°C for 45 min. To this reaction mixture at -78°C was added 2.58 mL (11.1 mmol) of tri-isopropyl borate, followed by slow warming of the mixture to room temperature (RT) over a period of 16 h. The reaction mixture was diluted with water and made basic with 2N NaOH solution. The mixture was then washed with EtOAc. The aqueous fraction was acidified with 2N HCl solution and stirred for 1 h at RT. The reaction mixture was extracted with EtOAc and the organic fractions were washed with water and saturated NaCl solution (brine), dried over Na_2SO_4 and filtered. The filtrate was concentrated to give the title compound as a white solid. ^{1}HNMR ($CDCl_3$) (δ, ppm): 7.96 (dd, *J*=

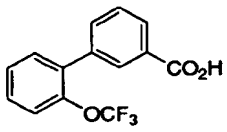
7.2, 1.6 Hz, 1 H), 7.53 (ddd, J = 9.1, 7.3, 1.8 Hz, 1 H), 7.38 (td, J = 7.3, 0.7 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 1 H), 5.25 (br s, 2H). MS (M+H): 206.9.

Step B: Ethyl-3-(2-Trifluoromethoxyphenyl)-benzoate



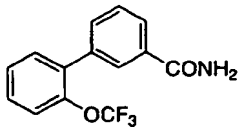
To a solution of 0.94 g (4.58 mmol) of ethyl-3-bromobenzoate in 14.5 mL of toluene at RT was added 0.25 g (0.218 mmol) of tetrakis(triphenylphosphine) palladium(0), 0.94 g (4.58 mmol) of 2-trifluoromethoxyphenylboronic acid, 2.22 mL (4.45 mmol) of 2M aqueous sodium carbonate solution and 7 mL of ethanol. The reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled and diluted with ethyl acetate and water. The organic fraction was separated and washed with saturated NaCl solution (brine), dried over $MgSO_4$, and filtered. The filtrate was concentrated to an oil which was purified by chromatography (silica, 1%, 5%, 30% successively ethyl acetate: hexanes) to give the title compound. ^{1}H NMR (CD_3OD) (δ, ppm): 8.02 (s, 1H), 7.97 (dd, J = 7.8, 1.2 Hz, 1H), 7.60 (dd, J = 7.7, 1.3 Hz, 1H), 7.50-7.33 (m, 5H), 4.31(q, 2H), 1.31(t, 3H). Mass Spectrum (ESI) m/e (M+1): 311.2.

Step C: 3-(2-Trifluoromethoxyphenyl)-benzoic acid



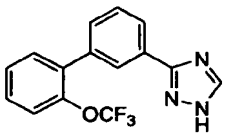
A solution of 0.3 g (4.19 mmol) of ethyl-3-(2-trifluoromethoxyphenyl) –benzoate and 8.3 mL (8.3 mmol) of a 1N solution of NaOH in 12.5 mL of methanol was stirred 18 h at RT. The reaction mixture was concentrated and the pH was adjusted to pH of 2 with 1 N HCl solution. The mixture was extracted with ethyl acetate (EtOAc) and the organic fraction was dried over $MgSO_4$ and filtered. The filtrate was concentrated to give the title compound as a white solid that was used without further purification.

Step D: 3-(2-Trifluoromethoxyphenyl)-benzamide



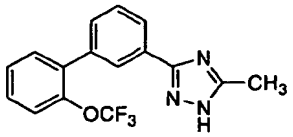
To a solution of 0.94 g (3.36 mmol) of 3-(2-trifluoromethoxyphenyl)-benzoic acid in 17 mL of DMF was added 0.55 g (3.36 mmol) of carbonyldiimidazole (CDI) and the reaction was stirred at RT for 4 h. To the reaction mixture was added 2.6 g (33.6 mmol) of ammonium acetate and the reaction mixture was stirred over night at RT. The reaction mixture was partitioned between ethyl acetate and water and the organic fraction was washed with brine, dried over $MgSO_4$, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 30%, 50% successively EtOAc: hexanes) to give the title compound. Mass Spectrum (ESI) m/e (M+1): 282.2.

Step E: 3-[3-(2-Trifluoromethoxyphenyl)-phenyl]-1,2,4-triazole



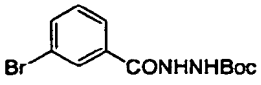
A solution of 0.137 g (0.48 mmol) of 3-(2-trifluoromethoxyphenyl)-benzamide in 1 mL of N,N-dimethylformamide dimethyl acetal was heated at 120 °C for 2 h at which time the reaction was concentrated *in vacuo*. To this material in 2.3 mL of acetic acid was added 0.028 g (0.55 mmol) of hydrazine hydrate and the reaction mixture was heated at 90 °C for 2 h. The reaction mixture was then concentrated and partitioned between EtOAc and saturated $NaHCO_3$ solution. The organic fraction was washed with brine, dried over $MgSO_4$, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 30:1, 9:1, 3:1 successively CH_2Cl_2: acetone) to give the title compound. ^1H NMR (CD_3OD) (δ, ppm): 8.32 (s, 1H), 8.06 (s, 1H), 7.98 (m, 1H), 7.50 (m, 3H), 7.39(m, 3H). Mass Spectrum (ESI) m/e (M+1): 306.1.

REFERENCE EXAMPLE 2



5-Methyl-3-[3-((2-trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole

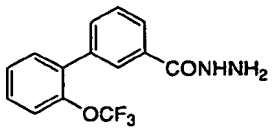
Step A: 3-Bromophenylcarbonyl-(N-t-butoxycarbonyl)hydrazide



A solution of 1 g (4.97 mmol) of 3-bromobenzoic acid, 0.59 g (4.52 mmol) of t-butylcarbazate, 0.95 g (4.97 mmol) of EDC [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide), 0.67 g (4.97 mmol) of hydroxybenzotriazole (HOBt) and 3.15 mL (18.1 mmol) of diisopropylethylamine in 23 mL of CH_2Cl_2 was stirred at RT for 18 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1N HCl solution, saturated $NaHCO_3$ solution and brine. The solution was dried over $MgSO_4$, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 30:1, 9:1, 3:1 successively CH_2Cl_2:acetone) to give the title compound.

Mass Spectrum (ESI) m/e (M): 314.0, (M+2): 316.0

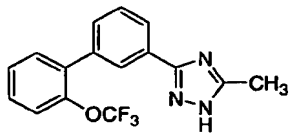
Step B: 3-((2-Trifluoromethoxy)phenyl)-phenylhydrazide



A solution of 0.22 g (1.07 mmol) of 2-trifluoromethoxyphenylboronic acid and 0.32 g (1.02 mmol) of 3-bromophenylcarbonyl-N-t-butoxycarbonylhydrazide in 5 mL of toluene and 2.5 mL of n-propanol was stirred for 30 min. To this reaction mixture was added 0.0007 g (0.003 mmol) of palladium acetate, 0.0024 g (0.009 mmol) of triphenylphosphine and 0.61 mL (1.2 mmol) of a 2M aqueous sodium carbonate solution and the reaction mixture was heated at reflux for 18 h. The reaction mixture was cooled and diluted with EtOAc and water. The

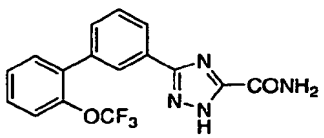
organic fraction was dried over $MgSO_4$, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 30:1, 9:1 successively, CH_2Cl_2: acetone) to give the protected hydrazide which was then dissolved in a mixture of 2.1 mL of TFA and 2.1 mL of CH_2Cl_2. The reaction mixture was stirred for 2 h whereupon it was concentrated, dissolved in CH_2Cl_2 and washed with 1N NaOH solution. The organic fraction was dried over $MgSO_4$, filtered and the filtrate was concentrated to give the tile compound as a white solid. Mass Spectrum (ESI) m/e (M+1): 297.1.

Step C: 5-Methyl-3-[3-((2-trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole



To a solution of 0.093 g (0.98 mmol) of acetamidine hydrochloride in 1.1 mL of ethanol was added 0.22 mL (0.98 mmol) of a 25% solution of sodium methoxide in methanol and the reaction mixture was stirred for 30 min. whereupon it was filtered. To the filtrate was added 0.19 g (0.66 mmol) of 3-((2-trifluoromethoxy) phenyl)-bromophenylhydrazide and the reaction mixture was stirred over night. The reaction mixture was concentrated and purified by chromatography (silica, 3%, 10%, 30% successively, methanol: CH_2Cl_2) to give a white solid. The white solid was heated (neat) to its melting temperature for 30 min. The reaction was cooled to RT, dissolved in CH_2Cl_2 and concentrated. The residue was purified by chromatography (silica, 3%, 10%, successively, methanol: CH_2Cl_2) to give the title compound as a white solid. ^1H NMR (CD_3OD) (δ, ppm): 8.00 (s, 1H), 7.93 (m, 1H), 7.49 – 7.34 (m, 6H), 2.41(s, 3H). Mass Spectrum (ESI) m/e (M+1): 320.5.

REFERENCE EXAMPLE 3



3-[3-((2-Trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-5-carboxamide

Step A. Ethyl-N^1-3-(2-trifluoromethoxy)-benzoyl-N^2-oxamidrazonate

To a solution of 0.45 g (1.54 mmol) of 3-(2-trifluoromethoxyphenyl)-bromophenylhydrazide (Example 9, Step B) in 20 mL of CH_2Cl_2 was added 0.54 g (2.3 mmol) of carbethoxy-S-methylthioformimidium tetrafluoroborate and and 0.43 mL (3.08 mmol) of triethylamine and the reaction was stirred at refluxing temperatures for 4 hr. The reaction mixture was cooled to RT, washed with water, dried over Na_2SO_4, filtered and the filtrate was concentrated to a solid. Two mL of CH_2Cl_2 was added and the resulting solid product was recovered by filtration. Mass Spectrum (ESI) m/e (M+1): 396.1.

Step B. 5-Ethyl-3-[3-((2-trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-5-carboxylate

The solid Ethyl-N^1-3-(2-trifluoromethoxy)-benzoyl-N^2-oxamidrazonate (0.25 g, 0.616 mmol) was heated in an oil bath above its melting point for 20 min. After cooling to RT, the residue was dissolved in CH_2Cl_2 and concentrated to give a yellow solid. It was purified by chromatography (silica, 10%, 30%, 50% successively, EtOAc: hexanes) to give a white solid. Mass Spectrum (ESI) m/e (M+1): 378.1.

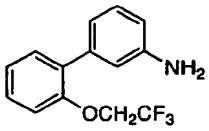
Step C. 3-[3-((2-Trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-5-carboxamide

A solution of 0.13 g (0.34 mmol) of 5-ethyl-3-[3-((2-trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole-5-carboxylate in 2 mL of methanol in a tube was saturated with ammonia. The tube was sealed and the reaction mixture was heated at 60 °C overnight. The reaction mixture was then concentrated and the residue was purified by chromatography (silica, 3%, 10%, 20% successively methanol: CH_2Cl_2) to give the title compound. ^{1}H NMR (CD_3OD) (δ, ppm): 8.10 (s, 1H), 8.02 (m, 1H), 7.54 – 7.36 (m, 6H). Mass Spectrum (ESI) m/e (M+1): 349.2.

REFERENCE EXAMPLE 4

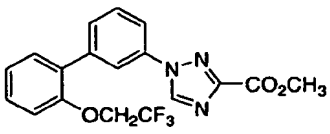
1-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

Step A. 3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-aniline



To a solution of 1.0 g (3.93 mmol) of 2-trifluoroethoxyphenyl bromide (Example 2, Step A) in 39 mL of toluene was added 0.136 g (0.118 mmol) of tetrakis(triphenylphosphine)palladium(0), 0.56 g (4.31 mol) of 3-aminophenylboronic acid, 47 mL (94.1 mmol) of a 2M solution of sodium carbonate and 8 mL of ethanol and the reaction mixture was heated at 90 °C for 22 hr. The reaction mixtur was colld to RT, and partitioned between water and EtOAc. The aqueous fraction was extracted with EtOAc nd the combined organic fractions were washed with water and brine and dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 4:1 hexanes: EtOAc) to give the title compound. Mass Spectrum (ESI) m/e M+1 268.1.

Step B. Methyl-1-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxylate



To a solution of 0.923 g (3.45 mmol) of 3-((2-trifluoroethoxy)-phenyl)analine in 6 mL of a 1N solution of HCl at 0 °C was added 0.238 g (3.45 mmol) of sodium nitrite and 1 mL of water and the reaction mixture was stirred for 20 min. to give the diazonium salt solution.

To a solution of 0.27 g (2.76 mmol) of methylisocyanoacetate in 15 mL of methanol and 2 mL of water at 0 °C was added 1.8 g (22.08 mmol) of sodium acetate. To this reaction mixture was added dropwise the diazonium salt solution and the reaction mixture was

stirred at 0 °C for 1 h. The reaction mixture was then diluted with methanol and concentrated. The residue was diluted with EtOAc and 0.5N HCl solution. The aqueous layer was extracted with EtOAc and the combined organic fractions were washed with 5% $NaHCO_3$ solution, brine, dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, 1:1 EtOAc: hexanes) to give the title compound. Mass Spectrum (ESI) m/e M+1 378.1.

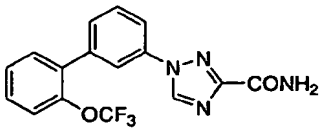
Step C. 1-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxylic acid

A solution of 0.29 g (0.769 mmol) of methyl-1-[3-((2-trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxylate and 2.2 mL (2.2 mmol) of a 1M solution of NaOH in water was stirred for 18 hr at RT. The reaction mixture was concentrated. The residue was diluted with water and the pH was adjusted to 2-4 with 1N HCl solution. The mixture was extracted with EtOAc and the combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated to give the title compound. Mass Spectrum (ESI) m/e M+1 363.9.

Step D. 1-[3-((2-(2,2,2-Trifluoroethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

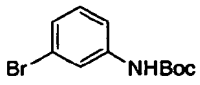
To a solution of 0.225 g (0.619 mmol) of 1-[3-((2-trifluoroethoxy) phenyl)-phenyl]-1,2,4-triazole-3-carboxylic acid in 3.1 mL of DMF was added 0.1 g (0.19 mmol) of CDI and the reaction mixture was stirred at RT for 4 hr. To the reaction mixture was added 0.477 g (6.19 mmol) of ammonium acetate and the reaction mixture was stirred for 19 hr. The reaction mixture was diluted with water and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic fractions were washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by chromatography (silica,1:1 EtOAc: hexanes, 1% methanol: CH_2Cl_2, 10% methanol: CH_2Cl_2) to give the title compound. Mass Spectrum (ESI) m/e M+1 363.1.

REFERENCE EXAMPLE 5



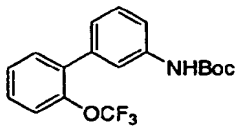
1-[3-((2-Trifluoromethoxy)-phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

Step A. 1-N-t-butoxycarbonylamino-3-bromobenzene



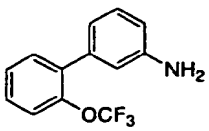
A solution of 10 g (58.13 mmol) of 3-bromoaniline and 15.2 g (69.75 mmol) of Boc_2O in 300 mL of toluene was heated overnight at 70 °C. The reaction mixture was concentrated and diluted with EtOAc and 0.5N HCl solution. The organic fraction was washed with 0.5N HCl solution and brine. It was dried over Na_2SO_4, filtered and the filtrate was concentrated. The residue was purified by chromatography (hexanes, 9:1 hexanes: EtOAc successively) to give the title compound.

Step B. 1-N-t-butoxycarbonyl-3-((2-Trifluoromethoxy)-phenyl)analine



1-N-t-Butoxycarbonylamino-3-bromobenzene was coupled with 2-trifluromethoxyphenylboronic acid according to procedures described in Reference Example 4, Step A.

Step C. 3-((2-Trifluoromethoxy)-phenyl)aniline



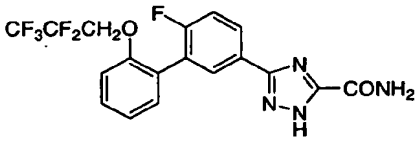
A solution of 0.977 g (2.77 mmol) of 1-N-t-butoxycarbonyl-3-((2-Trifluoromethoxy)-phenyl)analine in 7 mL of TFA and 7 mL of CH_2Cl_2 was stirred at RT for 1 hr. The reaction mixture was concentrated and the residue was diluted with 1N NaOH solution and EtOAc. The organic fraction was washed with 1N NaOH solution and brine, dried over Na_2SO_4 filtered and the filtrate was concentrated to give the title compound. Mass Spectrum (ESI) m/e M+1 254.1.

Step D. 1-[3-((2-Trifluoromethoxy)phenyl)-phenyl]-1,2,4-triazole-3-carboxamide

The title compound was prepared from 3-((2-Trifluoromethoxy)phenyl)aniline according to procedures described in Reference Example 4. Mass Spectrum (ESI) m/e M+1 349.1.

The following examples were prepared according to produres previously described and are provided to illustrate the present invention are not to be construed as limiting the scope of the invention in any manner.

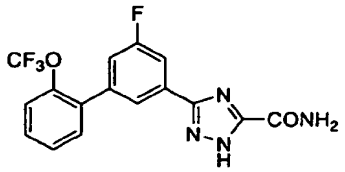
EXAMPLE 1



5-[6-Fluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 431.1.

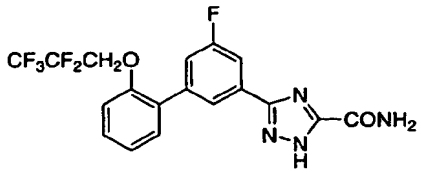
EXAMPLE 2



5-[5-Fluoro-2'-(trifluoromethoxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 367.0.

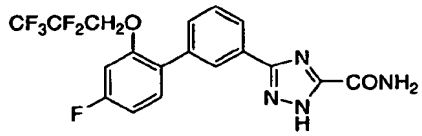
EXAMPLE 3



5-[5-Fluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 431.0.

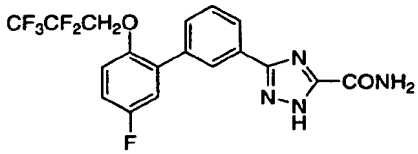
EXAMPLE 4



5-[4'-Fluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 431.0.

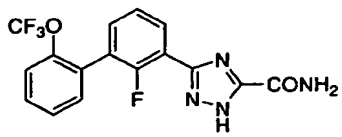
EXAMPLE 5



5-[5'-Fluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 431.1.

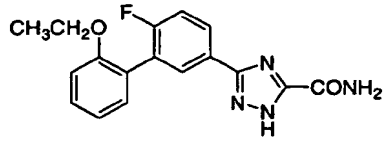
EXAMPLE 6



5-[2-Fluoro-2'-(trifluoromethoxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 367.0.

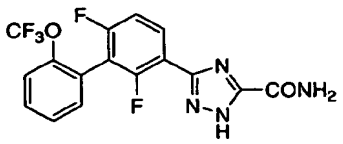
EXAMPLE 7



5-[6-Fluoro-2'-(ethoxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 381.1.

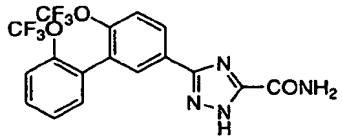
EXAMPLE 8



5-[2,6-Difluoro-2'-(trifluoromethoxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 385.0.

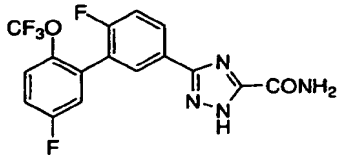
EXAMPLE 9



5-[2',6-Bis(trifluoromethoxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 432.9.

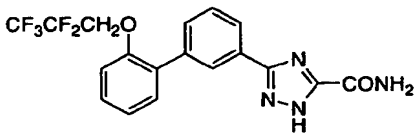
EXAMPLE 10



5-[5',6-Difluoro-2'-(trifluoromethoxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 384.9.

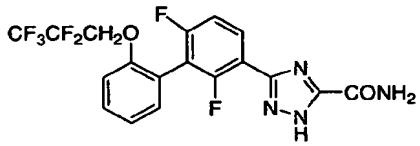
EXAMPLE 11



5-[2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

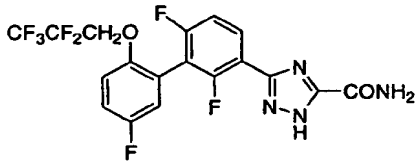
Mass Spectrum (ESI) m/e (M+1): 413.2.

EXAMPLE 12



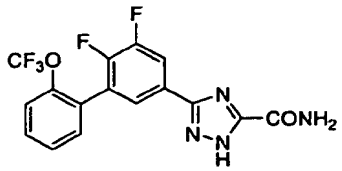
5-[2,6-Difluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

EXAMPLE 13



5-[2,5',6-Trifluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

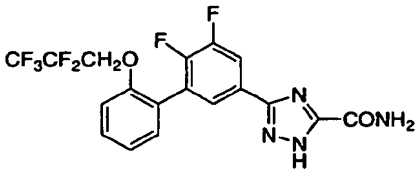
EXAMPLE 14



5-[5,6-Difluoro-2'-(trifluoromethoxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

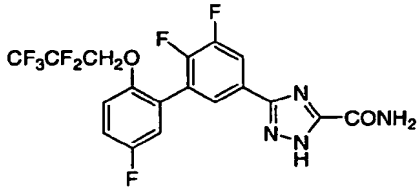
Mass Spectrum (ESI) m/e (M+1): 385.0.

EXAMPLE 15



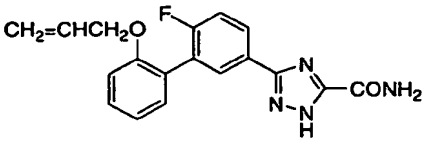
5-[5,6-Difluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

EXAMPLE 16



5-[5,5',6-Trifluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

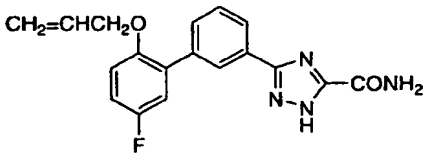
EXAMPLE 17



5-[6-Fluoro-2'-(allyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 339.1.

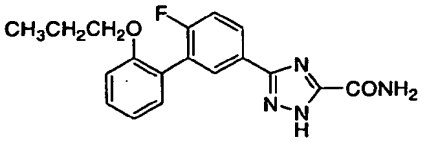
EXAMPLE 18



5-[5'-Fluoro-2'-(allyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 339.2.

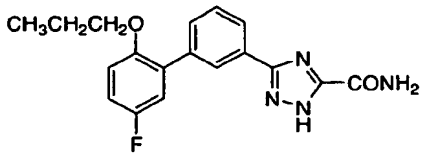
EXAMPLE 19



5-[6-Fluoro-2'-(n-propyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

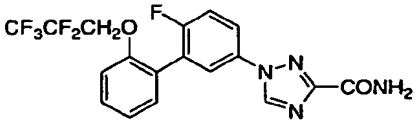
Mass Spectrum (ESI) m/e (M+1): 341.1.

EXAMPLE 20



5-[5'-Fluoro-2'-(n-propyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

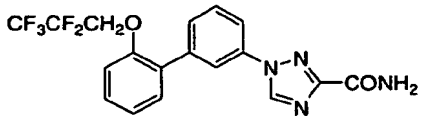
EXAMPLE 21



1-[6-Fluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 430.9.

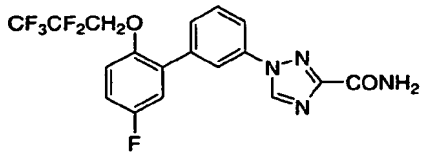
EXAMPLE 22



1-[2'-(2,2,3,3,3-Pentafluoropropyloxy)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 413.0.

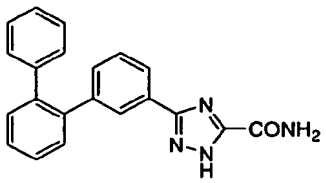
EXAMPLE 23



1-[5'Fluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide

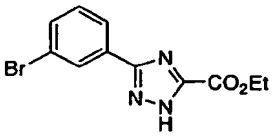
Mass Spectrum (ESI) m/e (M+1): 431.0.

EXAMPLE 24



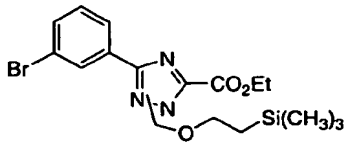
5-[2'-(Phenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Step A. Ethyl-5-[3-bromophenyl]2*H*-1,2,4-triazole-3-carboxylate



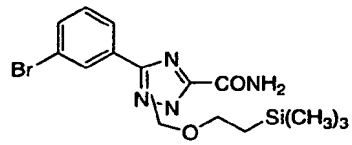
The title compound was prepared from ethyl-3-bromobenzoate according to procedures described in Reference Example 3.

Step B. Ethyl-2-trimethylsilylethoxymethyl-5-[3-bromophenyl]-1,2,4-triazole-3-carboxylate



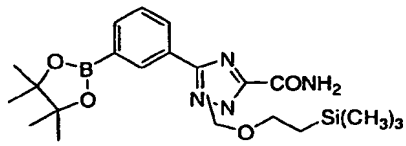
To a mixture of 0.79 g (19.8 mmol) of sodium hydride (60% in oil) in 15 mL of THF at 0 °C was added dropwise a solution of 5.31 g (18 mmol) of ethyl-5-[3-bromophenyl]2*H*-1,2,4-triazole-3-carboxylate in 80 mL of THF. After stirring for 10 min at RT, the reaction mixture was cooled to 0 °C and to it was added dropwise 3 g (18 mmol) of trimethylsilylethoxy methyl chloride (SEM-Cl). After stirring for 2 hr, the reaction mixture was poured into water and extracted with ethyl acetate. The combined organic fractions were washed with brine, dried ($MgSO_4$) filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, ethyl acetate: hexanes, 10-25% gradient) to give the title compound as a mixture of two regiosiomers.

Step C. 2-Trimethylsilylethoxymethyl-5-[3-bromophenyl]-1,2,4-triazole-3-carboxamide



A solution of 4.39 g (10.3 mmol) of ethyl-2-trimethylsilylethoxymethyl-5-[3-bromophenyl]-1,2,4-triazole-3-carboxylate in 10 mL of a 2N solution of ammonia in methanol was stirred overnight at 60 °C. The reaction mixture was then concentrated to give the title compound.

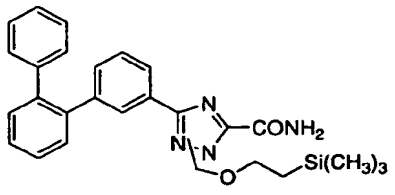
Step D. 2-Trimethylsilylethoxymethyl-5-[3-(pinicolboranyl)phenyl]-1,2,4-triazole-3-carboxamide



To a mixture of 7.1 g (17.9 mmol) of 2-Trimethylsilyl ethoxymethyl-5-[3-bromophenyl]-1,2,4-triazole-3-carboxamide and 9.1 g (35.8 mmol) of pinicolboron (4,4,5,5-tetramethyl-1,3,2-dioxaborolane) in 150 mL of DMSO at RT was added 7 g (71.5 mmol) of

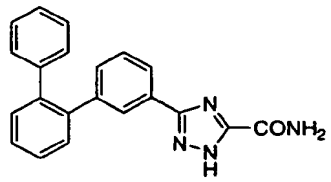
potassium acetate and the reaction was stirred at 40 °C for 15 min in a nitrogen atmosphere. To the reaction mixture was added 2.92 g (3.58 mmol) of $PdCl_2$(dppf) and the reaction mixture was stirred for 18 hr at 95-100 °C. The reaction mixture was cooled and partitioned between EtOAc and water. The organic fraction was washed with water and brine, dried($MgSO_4$), filtered and the filtrate was concentrated. The residue was purified by chromatography (silica, ethyl acetate: hexanes, 0-25% gradient) to give the title compound.

Step E. 2-Trimethylsilylethoxymethyl-5-[2'-(Phenyl)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide



To a mixture of 0.0385 g (0.082 mmol) of 2-Trimethylsilyl ethoxymethyl-5-[3-(pinicolboranyl)phenyl]-1,2,4-triazole-3-carboxamide, 0.0297 g (0.128 mmol) of 2-bromobiphenyl, 0.128 mL (0.255 mmol) of a 2M solution of sodium carbonate in 1.5 mL of toluene and 0.5 mL of ethanol was added 0.013 g (0.011 mmol) of Pd $(PPh_3)_4$ and the reaction mixture was stirred at 100 °C for 6 hr. The reaction mixture was cooled to RT and partitioned between EtOAc and water. The organic fraction was washed with brine, dried ($MgSO_4$), filtered and the filtrate was concentrated. The residue was purifed by chromatography (silica, Hexanes: EtOAc, 0-50% gradient) to give the title compound.

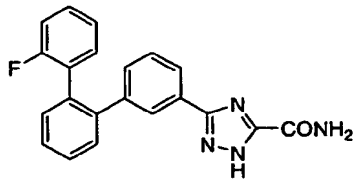
Step F. 5-[2'-(Phenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide



A mixture of 0.035 g of 2-Trimethylsilylethoxymethyl-5-[2'-(Phenyl)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide in 3 mL of acetonitrile and 9 mL of a 50% solution of HF in water was stirred at rt for 6 hours. The reaction mixture was then concentrated and the residue was purified by chromatography (silica, CH_3OH: CH_2Cl_2 0-5% gradient) to give the title compound.

Mass Spectrum (ESI) m/e (M+1): 341.2.

EXAMPLE 25

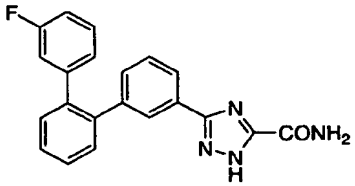


5-[2'-(2-Fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

The title compound was prepared according to procedures described in Example 24. 2'-Fluoro-2-bromobiphenyl was prepared from 2-fluorophenylboronic acid and 2-bromophenyliodide according to the procedure described in Example 24, Step D.
Mass Spectrum (ESI) m/e (M+1): 359.2.

The following Examples 26 to 33 were prepared according to procedures described in Examples 24 and 25.

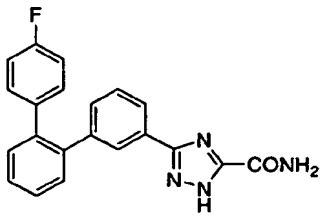
EXAMPLE 26



5-[2'-(3-Fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 359.2.

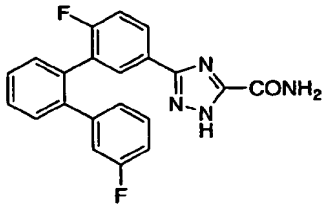
EXAMPLE 27



5-[2'-(4-Fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 359.2.

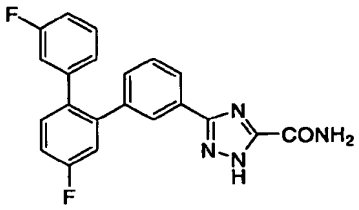
EXAMPLE 28



5-[6-Fluoro-2'-(3-fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 377.2.

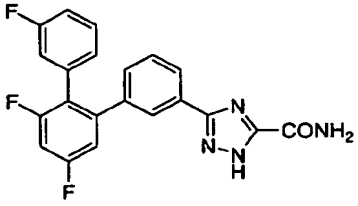
EXAMPLE 29



5-[5'-Fluoro-2'-(3-fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 377.2.

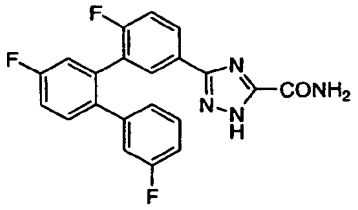
EXAMPLE 30



5-[3',5'-Difluoro-2'-(3-fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 395.03.

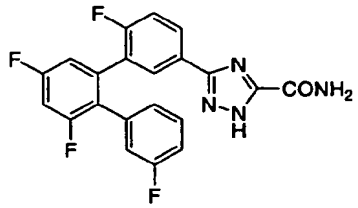
EXAMPLE 31



5-[6-Fluoro-5'-fluoro-2'-(3-fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 395.23.

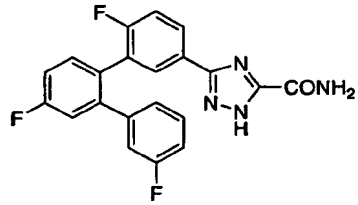
EXAMPLE 32



5-[6-Fluoro-3',5'-difluoro-2'-(3-fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 413.16.

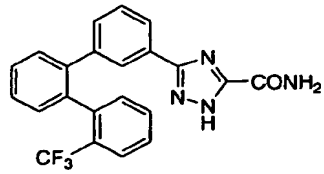
EXAMPLE 33



5-[6-Fluoro-4'-fluoro-2'-(3-fluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

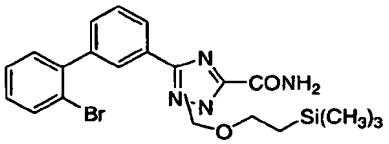
Mass Spectrum (ESI) m/e (M+1): 395.23.

EXAMPLE 34



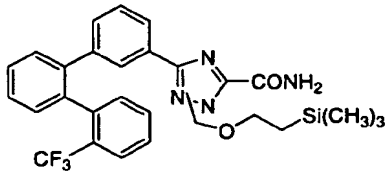
5-[2'-(2-trifluoromethylphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Step A. 2-Trimethylsilylethoxymethyl-5-[2'-(bromo)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide



The title compound was prepared from 2-Trimethylsilyl ethoxymethyl-5-[3-(pinicolboranyl)phenyl]-1,2,4-triazole-3-carboxamide (Example 24, Step D) and 2-bromophenyliodide according to procedures described in Example 24, Step E.

Step B. 2-Trimethylsilylethoxymethyl-5-[2'-(2-trifluoromethylphenyl) biphenyl-3-yl]-1,2,4-triazole-3-carboxamide



The title compound was prepared from 2-trimethylsilyl ethoxymethyl-5-[2'-(bromo)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide and 2-thrifluoromethylphenylboronic acid according to the Suzuki conditions described in the preceding examples.

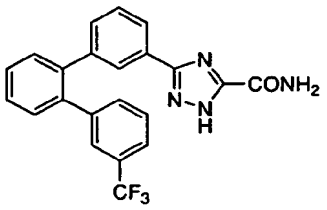
Step C. 5-[2'-(Trifluoromethylphenyl) biphenyl-3-yl]-1,2,4-triazole-3-carboxamide

The title compound was prepared from 2-Trimethylsilyl ethoxymethyl-5-[2'-(2-trifluoromethylphenyl) biphenyl-3-yl]-1,2,4-triazole-3-carboxamide according to procedures described in Example 24, Step F.

Mass Spectrum (ESI) m/e (M+1): 408.98.

The following Examples 35 to 42 were prepared according to procedures described in Examples 24 and 34.

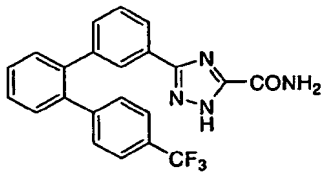
EXAMPLE 35



5-[2'-(3-Trifluoromethylphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 408.98.

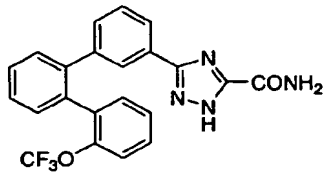
EXAMPLE 36



5-[2'-(4-Trifluoromethylphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 408.98.

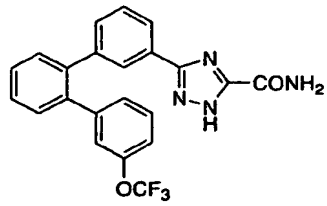
EXAMPLE 37



5-[2'-(2-Trifluoromethoxyphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 424.9.

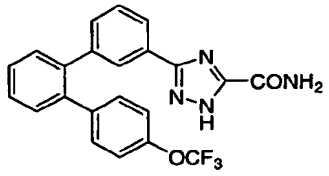
EXAMPLE 38



5-[2'-(3-Trifluoromethoxyphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 425.2.

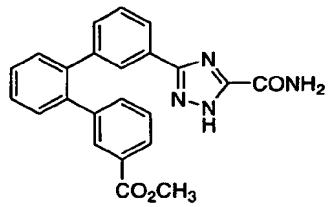
EXAMPLE 39



5-[2'-(4-Trifluoromethoxyphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 425.3.

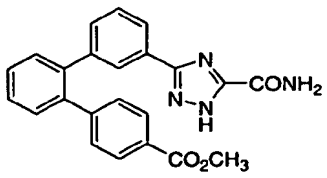
EXAMPLE 40



5-[2'-(3-Carbomethoxyphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 367.2 (M-OCH_3)

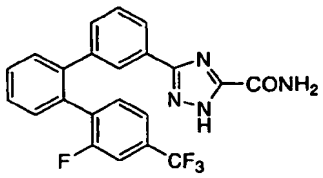
EXAMPLE 41



5-[2'-(4-Carbomethoxyphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 367.2 (M-OCH_3)

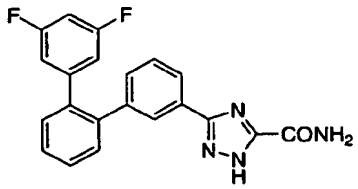
EXAMPLE 42



5-[2'-(2-Fluoro-4-trifluoromethylphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 427.1.

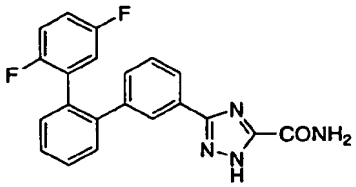
EXAMPLE 43



5-[2'-(3,5-Difluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 377.2.

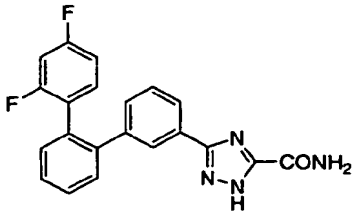
EXAMPLE 44



5-[2'-(2,5-Difluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 377.18.

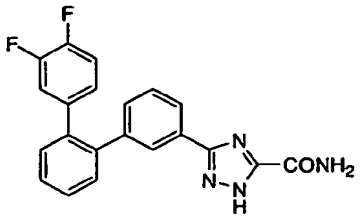
EXAMPLE 45



5-[2'-(2,4-Difluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 377.18.

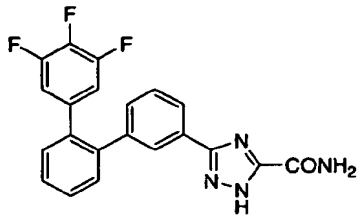
EXAMPLE 46



5-[2'-(3,4-Difluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 377.0.

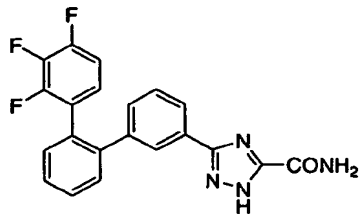
EXAMPLE 47



5-[2'-(3,4,5-Trifluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 396.15.

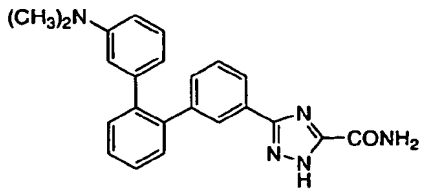
EXAMPLE 48



5-[2'-(2,3,4-Trifluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 396.2.

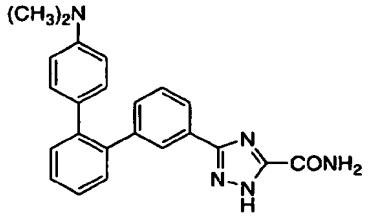
EXAMPLE 49



5-[2'-(3-Dimethylaminophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 384.3.

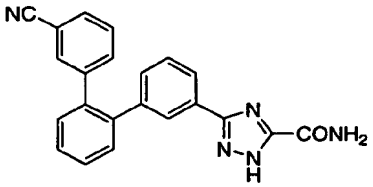
EXAMPLE 50



5-[2'-(4-Dimethylaminophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 383.9.

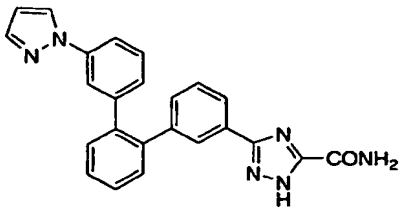
EXAMPLE 51



5-[2'-(3-Cyanophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 366.18.

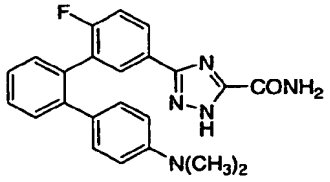
EXAMPLE 52



5-[2'-(3-(pyrazol-1-yl)phenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

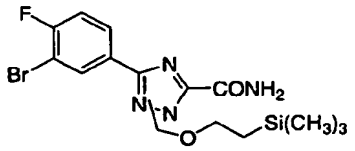
Mass Spectrum (ESI) m/e (M+1): 408.17.

EXAMPLE 53



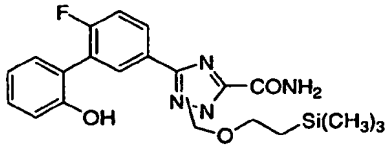
5-[6-Fluoro-2'-(4-dimethylaminophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Step A. 2-Trimethylsilylethoxymethyl-5-[3-bromo-6-fluorophenyl]-1,2,4-triazole-3-carboxamide



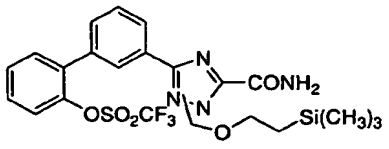
The title compound was prepared according to procedures described in Example 24.

Step B. 2-Trimethylsilylethoxymethyl-5-[2'-(hydroxy)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide



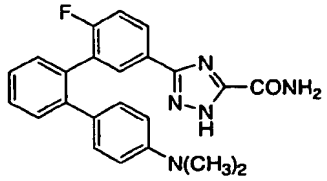
The title compound was prepared from 2-trimethylsilyl ethoxymethyl-5-[3-(pinicolboranyl)phenyl]-1,2,4-triazole-3-carboxamide (Example 24, Step D) and 2-bromophenyliodide according to procedures described in Example 24, Step E.

Step C. 2-Trimethylsilylethoxymethyl-5-[2'-(trifluoromethylsulfonyloxyphenyl) biphenyl-3-yl]-1,2,4-triazole-3-carboxamide



To a solution of 0.2 g (0.467 mmol) of 2-trimethylsilyl ethoxymethyl-5-[2'-(hydroxy)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide and 0.106 mL (0.61 mmol) of diisopropylethylamine in 10 mL of acetonitrile at 0 °C was added 0.217 g (0.61 mmol) of N-phenyltrifluoromethanesulfonamide and the reaction mixture was stirred at RT for 18 hr. The reaction mixture was concentrated and the residue was purified by chromatography (silica, CH_3OH: CH_2Cl_2, 0-6% gradient then 6% CH_3OH: CH_2Cl_2)

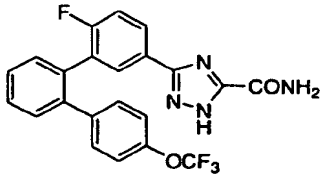
Step D. 5-[6-Fluoro-2'-(4-dimethylaminophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide



The title compound was prepared by first coupling trimethylsilylethoxymethyl-5-[2'-(trifluoromethylphenyl) biphenyl-3-yl]-1,2,4-triazole-3-carboxamide with 4-dimethylaminophenylboronic acid under standard Suzuki coupling conditions. Then the trimethylsilylethoxymethyl protecting group was removed as described in Example 24, Step F. Mass Spectrum (ESI) m/e (M+1): 402

The following Examples 54 to 56 were prepared according to procedures described in Example 53.

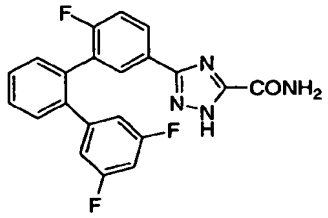
EXAMPLE 54



5-[6-Fluoro-2'-(4-trifluoromethoxyphenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 443.0.

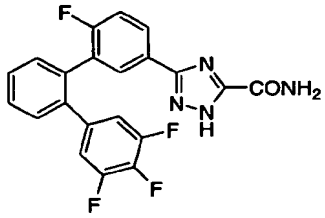
EXAMPLE 55



5-[6-Fluoro-2'-(3,5-difluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 395.18.

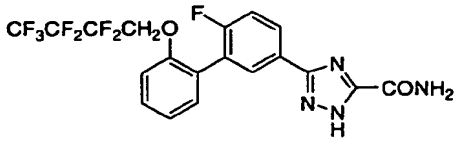
EXAMPLE 56



5-[6-Fluoro-2'-(3,4,5-trifluorophenyl)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 412.8.

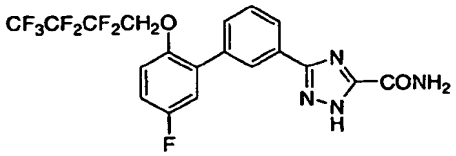
EXAMPLE 57



5-[6-Fluoro-5'-2'-(2,2,3,3,4,4,4-heptafluorobutyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 481.2.

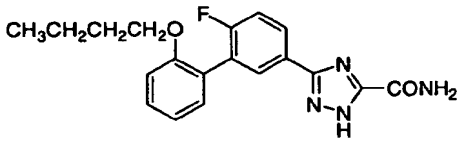
EXAMPLE 58



5-[5'-Fluoro-2'-(2,2,3,3,4,4,4-heptafluorobutyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 481.4.

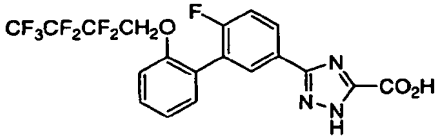
EXAMPLE 59



5-[6-Fluoro-2'-(n-butyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 355.3.

EXAMPLE 60



5-[5'-Fluoro-2'-(2,2,3,3,4,4,4-heptafluorobutyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxylic acid

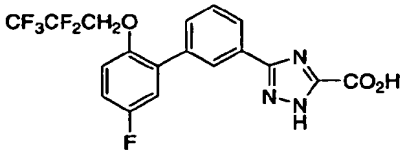
To a solution of 0.1 g (0.196 mmol) of ethyl 5-[5'-fluoro-2'-(2,2,3,3,4,4,4-heptafluorobutyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxylate (prepared according to procedures described in Reference Example 3, Step B) in 1.4 mL of methanol was added 0.59 mL (0.59 mmol) of a 1N aqueous solution of NaOH and the reaction mixture was stirred at rt for 23 hr. The pH of the reaction mixture was adjusted to pH = 4-5 with 1N HCl solution and the mixture was extracted with EtOAc. The organic fractions were dried (Na_2SO_4), filtered and the

filtrate was concentrated. The residue was purified by chromatography (silica, CH_2Cl_2: acetone 9:1, then CH_3OH: CH_2Cl_2 1 to 10% linear gradient) to give the title compound.

Mass Spectrum (ESI) m/e (M+1): 482.1.

The following Examples 61 – 63 were prepared according to procedures described in Reference Example 3, Step B.

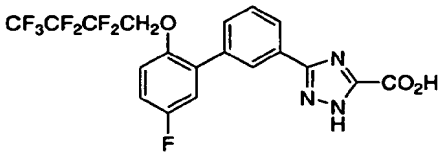
EXAMPLE 61



5-[5'-Fluoro-2'-(2,2,3,3,3-pentafluoropropyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxylate

Mass Spectrum (ESI) m/e (M+1): 432.1.

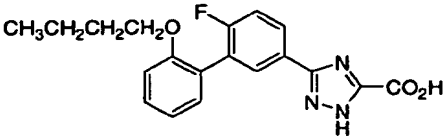
EXAMPLE 62



5-[5'-Fluoro-2'-(2,2,3,3,4,4,4-heptafluorobutyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxylate

Mass Spectrum (ESI) m/e (M+1): 482.3.

EXAMPLE 63

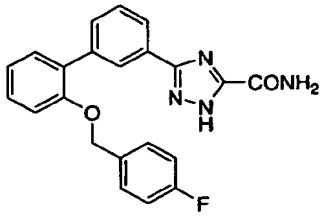


5-[6-Fluoro-2'-(n-butyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxylate

Mass Spectrum (ESI) m/e (M+1): 356.2.

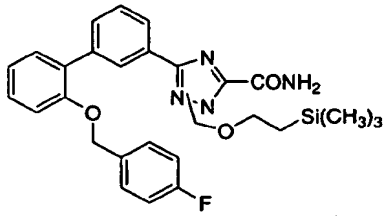
The following Examples 64 to 65 were prepared according to procedures described in Example 53.

EXAMPLE 64



5-[2'-(4-Fluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Step A. 2-Trimethylsilylethoxymethyl-5-[2'-(4-fluorobenzyloxy)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide



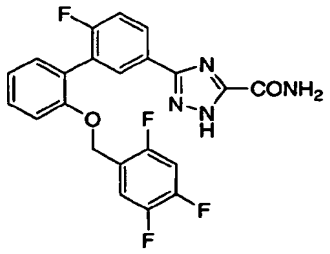
To a solution of 0.05 g (0.122 mmol) of 2-trimethylsilylethoxymethyl-5-[2'-(hydroxy)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide (prepared according to procedures described in Example 53) in 4 mL of DMSO was added 0.16 g (0.488 mmol) of cesium carbonate and the reaction mixture was stirred at rt for 20 min. To the reaction mixture was added 0.025 mL (0.244 mmol) of 4-fluorobenzylbromide and the reaction mixture was heated at 80 °C for 18 hr. The reaction mixture was partitioned between water and EtOAc. The organic fraction was washed with water and brine, dried ($MgSO_4$) and filtered. The filtrate was concentrated and the residue was purified by chromatography (silica, EtOAc: hexanes, 3:10) to give the title compound.

Step B. 5-[2'-(4-Fluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

The title compound was prepared from 2-trimethylsilylethoxymethyl-5-[2'-(4-fluorobenzyloxy)biphenyl-3-yl]-1,2,4-triazole-3-carboxamide according to procedures previously described. Mass Spectrum (ESI) m/e (M+1): 389.21.

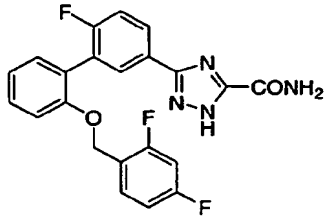
The following Examples 65 to 72 were prepared according to procedures described in Example 64.

EXAMPLE 65



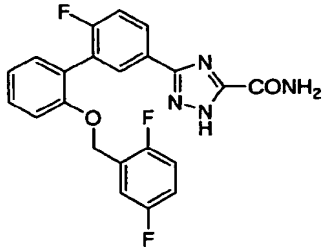
5-[6-Fluoro-2'-(2,4,5-trifluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide Mass Spectrum (ESI) m/e (M+1): 443.31.

EXAMPLE 66



5-[6-Fluoro-2'-(2,4-difluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide Mass Spectrum (ESI) m/e (M+1): 425.35.

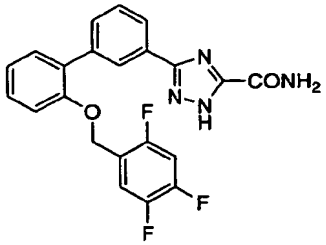
EXAMPLE 67



5-[6-Fluoro-2'-(2,5-difluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 425.35.

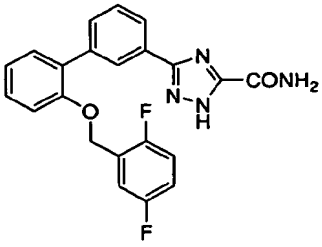
EXAMPLE 68



5-[2'-(2,4,5-Trifluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 424.91.

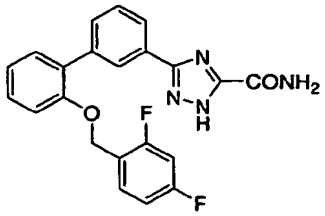
EXAMPLE 69



5-[2'-(2,5-Difluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 406.99.

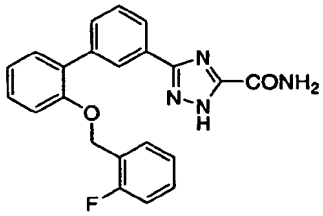
EXAMPLE 70



5-[2'-(2,4-Difluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 407.16.

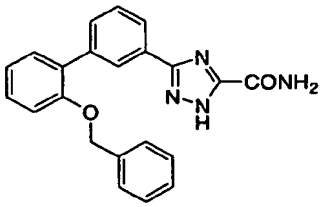
EXAMPLE 71



5-[2'-(2-Fluorobenzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

Mass Spectrum (ESI) m/e (M+1): 389.21.

EXAMPLE 72

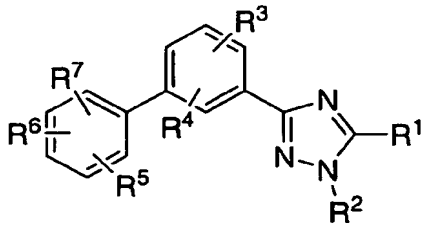


5-[2'-(Benzyloxy)biphenyl-3-yl]2*H*-1,2,4-triazole-3-carboxamide

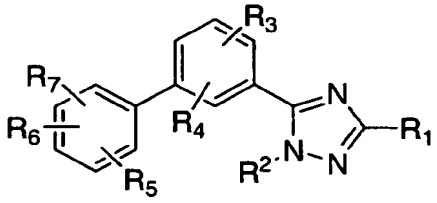
Mass Spectrum (ESI) m/e (M+1): 371.0.

WHAT IS CLAIMED IS:

1. A compound represented by Formula (I) or (II):



(I)



(II)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

(a) H,

(b) C_1-C_6-alkyl, C_2-C_4-alkenyl, C_2-C_4-alkynyl, any of which is optionally substituted with one or more of the following substituents: NR^aR^b, COOH, $CONR^aR^b$, or

(c) $-C(=O)R^a$, $COOR^a$, $CONR^aR^b$;

R^a is:

(a) H,

(b) C_1-C_6-alkyl, optionally substituted with one or more of halogen or CF_3, or

(c) CF_3;

R^b is

(a) H, or

(b) C_1-C_6-alkyl, optionally substituted with one or more of halogen or CF_3, or

(c) CF_3;

R^2 is H or C_{1-4} alkyl;

R^3 and R^4 each independently is:

(a) H,

(b) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl,

(c) halogen, or

(d) –C_1-C_6 alkyl, optionally substituted with one or more of halogen or CF_3; and

R^5, R^6 and R^7each independently is:

(a) H,

(b) -O- C_1-C_6-alkyl, -O- C_1-C_6-alkenyl, -O- C_1-C_6-alkynyl, any of which is optionally substituted with one or more of halogen or CF_3,

(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl,

(d) -O-phenyl, or -O-C_1-C_4-alkyl-phenyl, wherein phenyl is optionally substituted with 1-3 substituents selected from i) halogen, ii) -CN, iii) -NO_2, iv) CF_3, v) -OR^a, vi) -NR^aR^b, vii) –C_{0-4}alkyl-CO-OR^a, viii) -(C_{0-4}alkyl)-CO-N(R^a)(R^b), ix) and x) -C_{1-10} alkyl,wherein one or more of the alkyl carbons can be replaced by a –NR^a, C(O)-O-, or -N(R^a)-C(O)-N(R^a)-, or

(e) halogen, -OR^a, or phenyl wherein phenyl is optionally substituted with 1-3 substituents selected from i) halogen, ii) -CN, iii) –NO_2, iv) CF_3, v) pyrazolyl, vi) -OR^a, vii) -NR^aR^b, viii) -C_{0-4}alkyl-CO-OR^a, ix) -(C_{0-4}alkyl)-CO-N(R^a)(R^b), and x) –C_{1-10}alkyl, wherein one or more of the alkyl carbons can be replaced by a –NR^a, C(O)-O-, or -N(R^a)-C(O)-N(R^a)-.

2. The compound of Claim 1 described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H and is attached at the ortho position.

3. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted -O- C_1-C_6-alkyl.

4. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted phenyl.

5. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^5 is –O-C_1-C_4-alkyl-phenyl, wherein phenyl is optionally substituted.

6. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted –O-C_1-C_6-alkenyl.

7. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^6 is halogen.

8. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^3 is halogen.

9. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^3 and R^4 are halogen.

10. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4 and R^6 are halogen.

11. The compound of Claim 2, or a pharmaceutically acceptable salt thereof, wherein

R^3 is –O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl.

12. The compound of Claim 1 described by the chemical Formula (II), or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H and is attached at the ortho position.

13. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted -O- C_1-C_6-alkyl.

14. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted phenyl.

15. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^5 is –O-C_1-C_4-alkyl-phenyl, wherein phenyl is optionally substituted.

16. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted –O-C_1-C_6-alkenyl.

17. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^6 is halogen.

18. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^3 is halogen.

19. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^3 and R^4 are halogen.

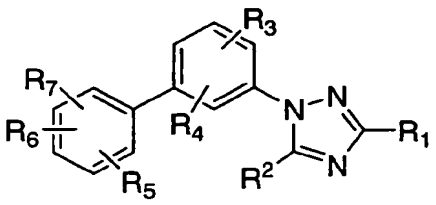
20. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^3, R^4 and R^6 are halogen.

21. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein

R^3 is $-O-C_0-C_4$-alkyl-C_1-C_4-perfluoroalkyl.

22. A compound represented by Formula (III)



(III)

or a pharmaceutically acceptable salt thereof, wherein $R^1 - R^7$ each is as defined in Claim 1.

23. The compound of Claim 22, or a pharmaceutically acceptable salt thereof, wherein

R^5 is other than H and is attached at the ortho position.

24. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted -O- C_1-C_6-alkyl.

25. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted phenyl.

26. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

R^5 is –O-C_1-C_4-alkyl-phenyl, wherein phenyl is optionally substituted.

27. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

R^5 is optionally substituted –O-C_1-C_6-alkenyl.

28. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

R^6 is halogen.

29. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

R^3 is halogen.

30. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

R^3 and R^4 are halogen.

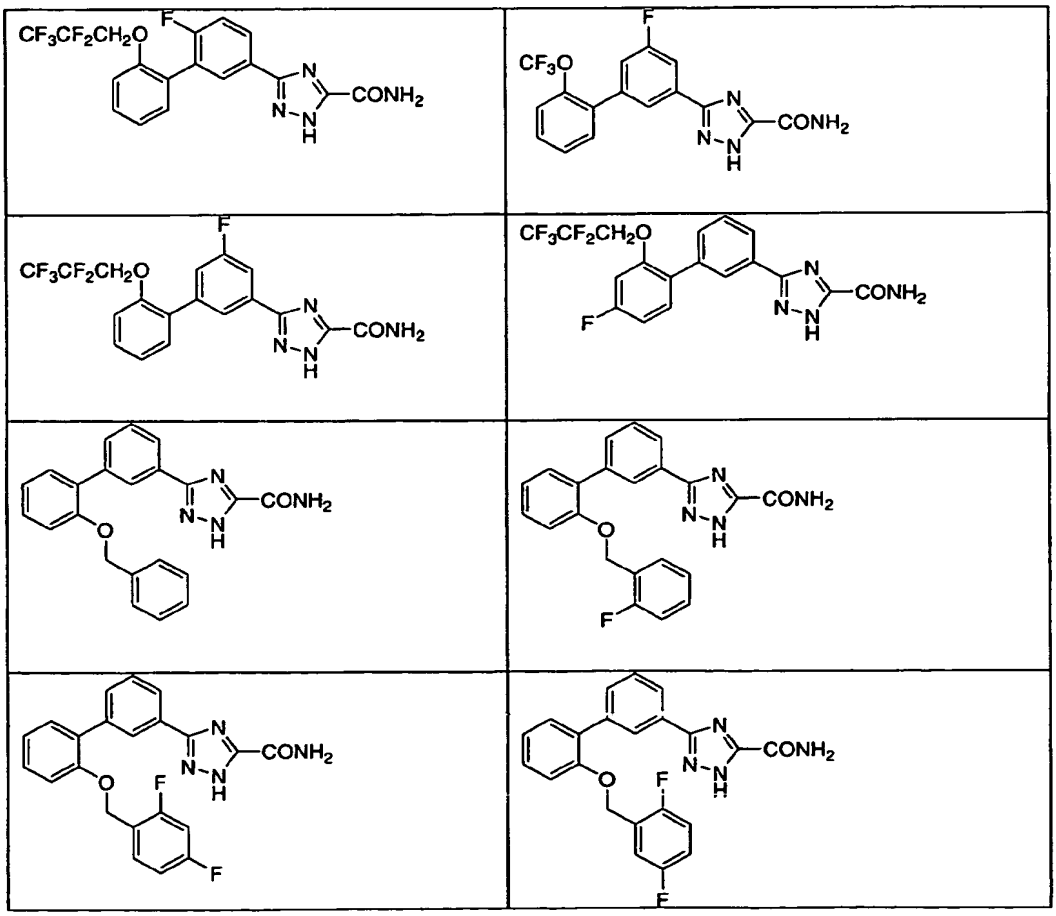
31. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

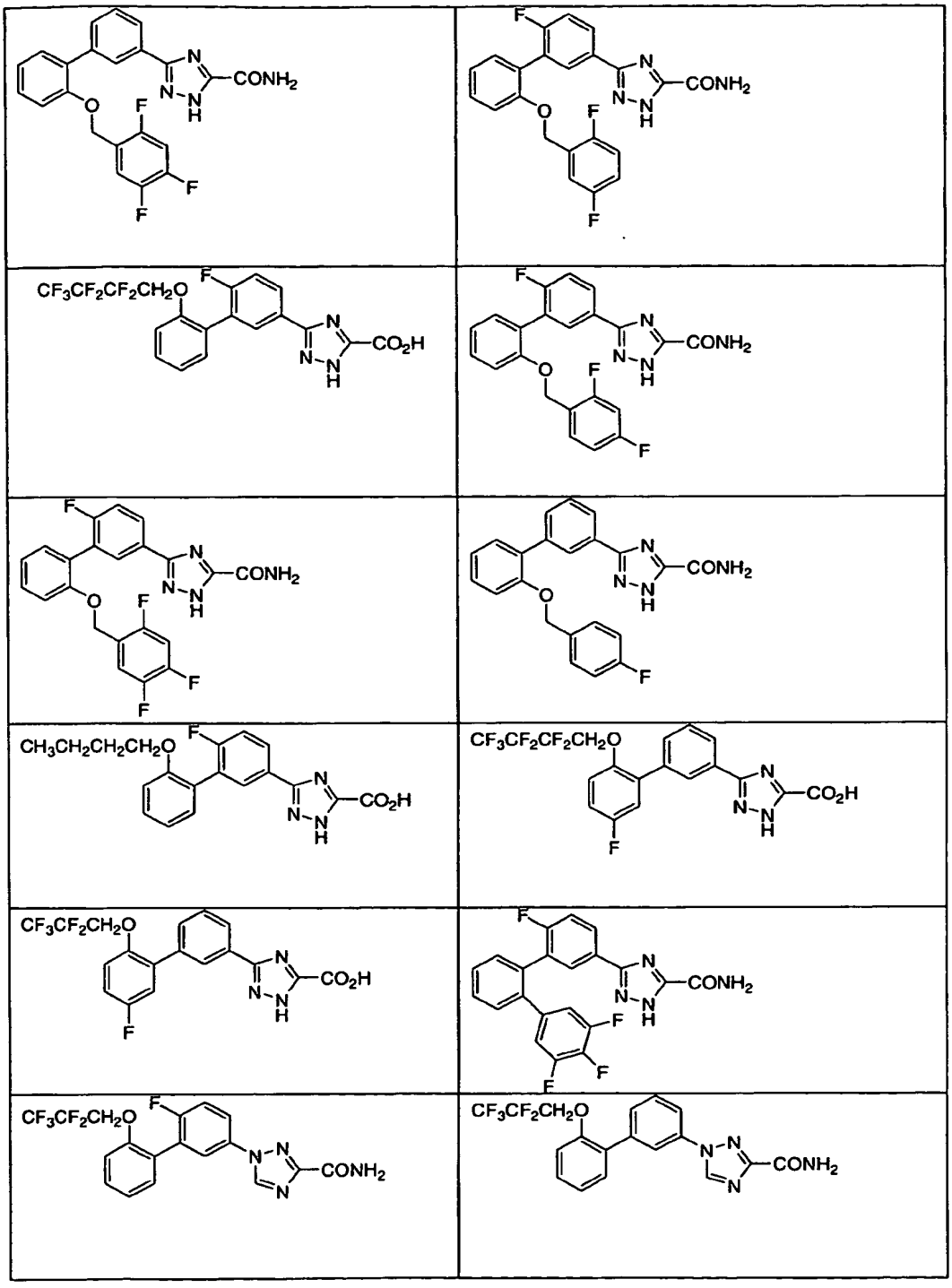
R^3, R^4 and R^6 are halogen.

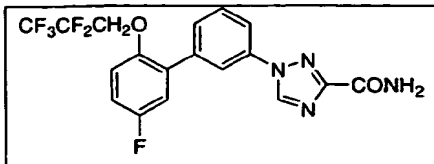
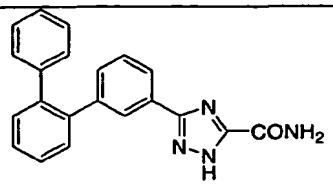
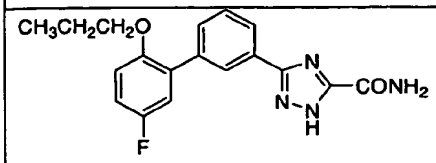
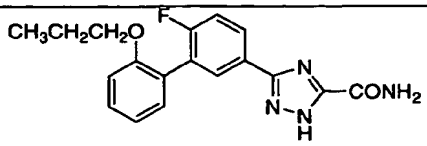
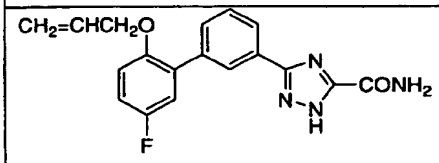
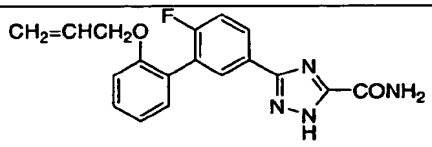
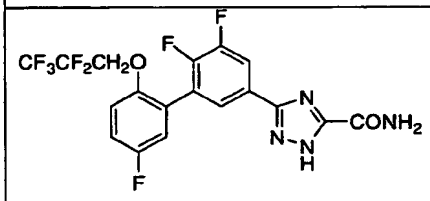
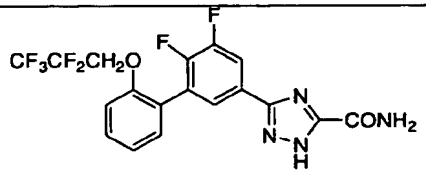
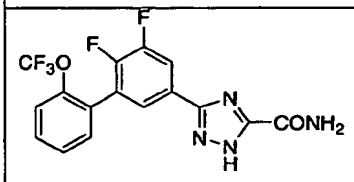
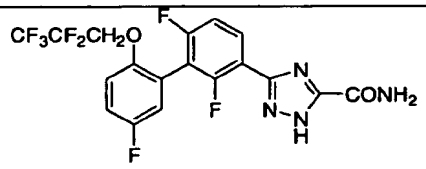
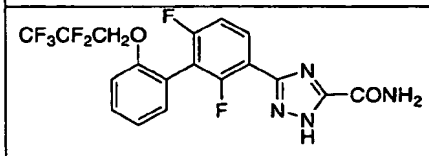
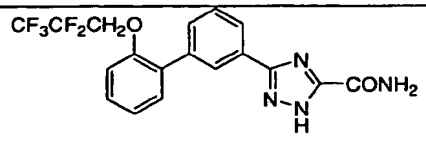
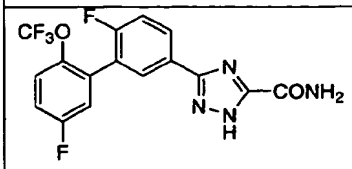
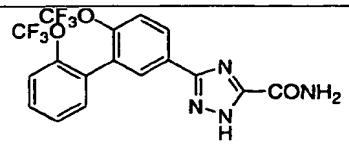
32. The compound of Claim 23, or a pharmaceutically acceptable salt thereof, wherein

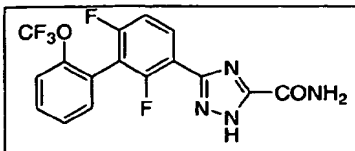
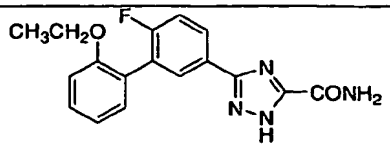
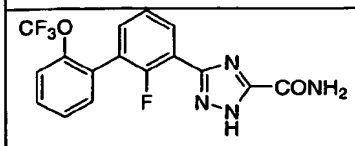
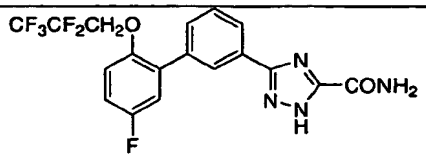
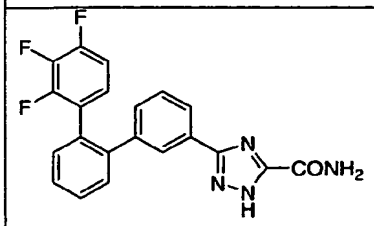
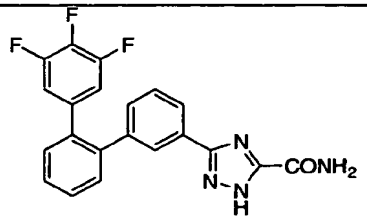
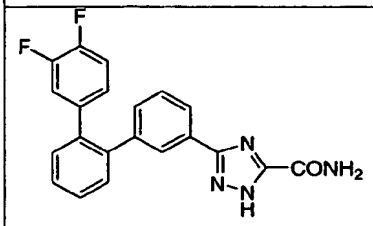
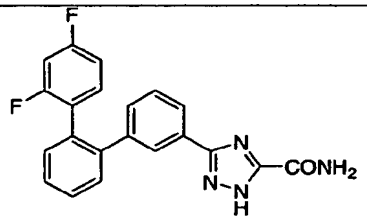
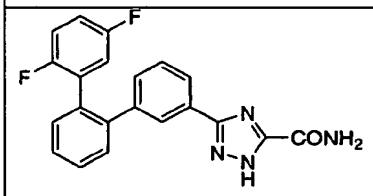
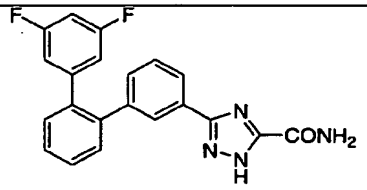
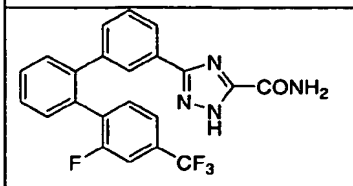
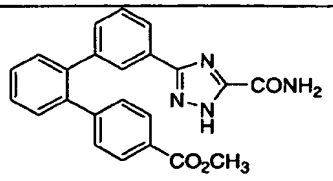
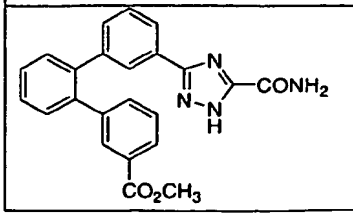
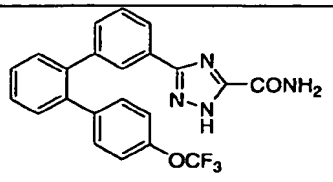
R^3 is –O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl.

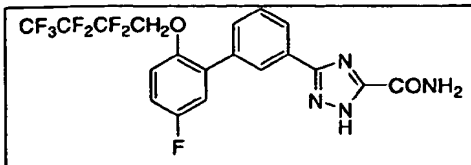
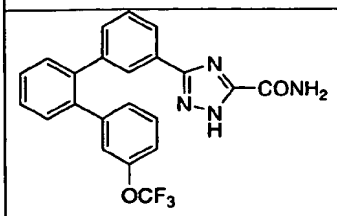
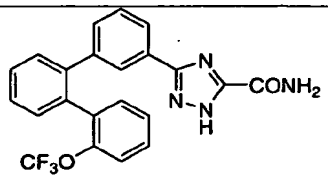
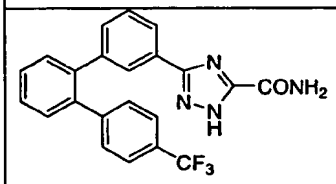
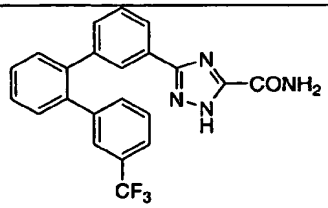
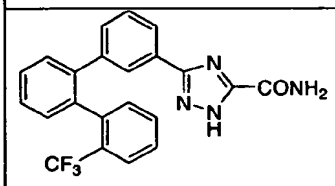
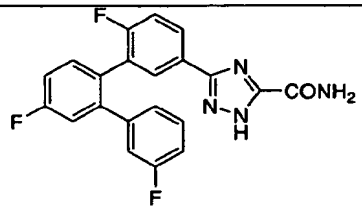
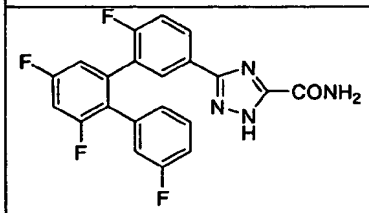
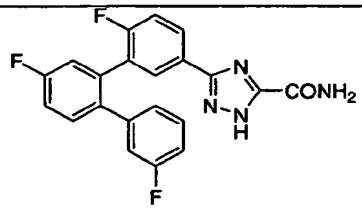
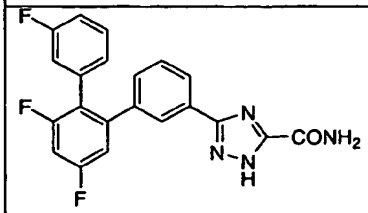
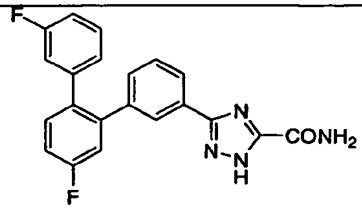
33. A compound represented by

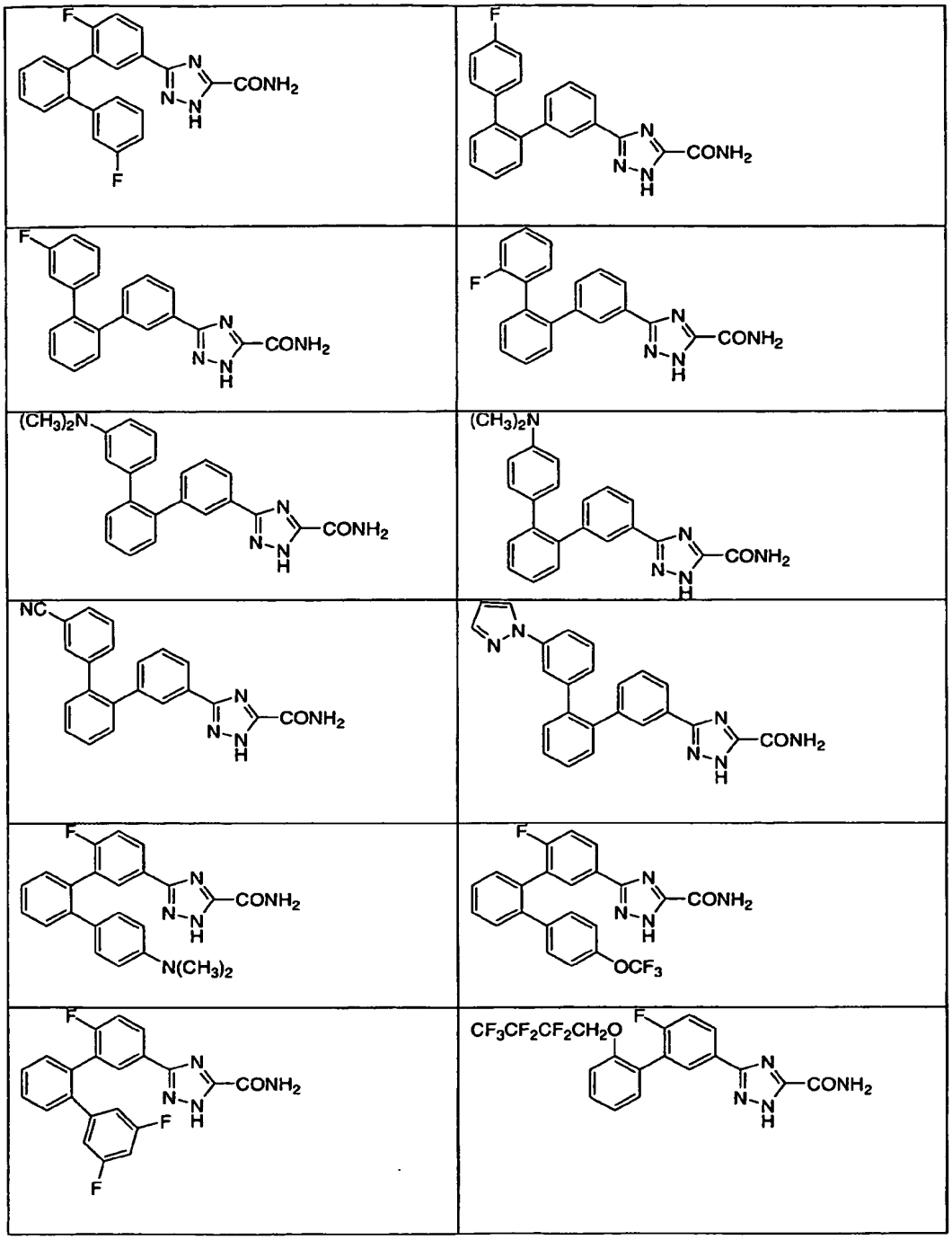


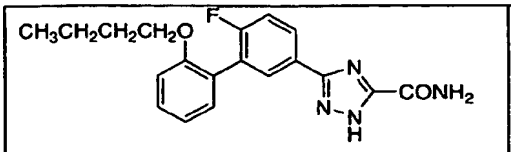




34. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

35. The pharmaceutical composition according to Claim 34, further comprising a second therapeutic agent selected from the group consisting of: i) opiate agonists, ii) opiate antagonists, iii) calcium channel antagonists, iv) 5HT receptor agonists, v) 5HT receptor antagonists vi) sodium channel antagonists, vii) NMDA receptor agonists, viii) NMDA receptor antagonists, ix) COX-2 selective inhibitors, x) NK1 antagonists, xi) non-steroidal anti-inflammatory drugs , xii) selective serotonin reuptake inhibitors , xiii) selective serotonin and norepinephrine reuptake inhibitors, xiv) tricyclic antidepressant drugs, xv) norepinephrine modulators, xvi) lithium, xvii) valproate, and xviii) neurontin.

36. A method of treatment or prevention of pain comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

37. A method of treatment or prevention of chronic, visceral, inflammatory and/or neuropathic pain syndromes comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

38. A method of treatment or prevention of pain resulting from, or associated with, traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, cancer and/or chemotherapy, comprising the step of administering

to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

39. A method of treatment or prevention of chronic lower back pain comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

40. A method of treatment or prevention of phantom limb pain comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

41. A method of treatment or prevention of HIV- and HIV treatment-induced neuropathy, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and/or related neuralgias comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

42. A method of administering local anesthesia comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

43. A method of treatment or prevention of irritable bowel syndrome and/or Crohn's disease comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

44. A method of treatment or prevention of epilepsy and/or partial and generalized tonic seizures comprising the step of administering to a patient in need thereof a

therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

45. A method for neuroprotection under ischaemic conditions caused by stroke or neural trauma comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

46. A method of treatment or prevention of multiple sclerosis comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

47. A method of treatment or prevention of bipolar disorder comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

48. A method of treatment or prevention of tachy-arrhythmias comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

49. A method of treatment or prevention of migraine, headache pain and/or migraine headache comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

50. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

51. The pharmaceutical composition according to Claim 49, further comprising a second therapeutic agent selected from the group consisting of: i) opiate agonists, ii) opiate antagonists, iii) calcium channel antagonists, iv) 5HT receptor agonists, v) 5HT receptor antagonists vi) sodium channel antagonists, vii) NMDA receptor agonists, viii) NMDA receptor antagonists, ix) COX-2 selective inhibitors, x) NK1 antagonists, xi) non-steroidal anti-inflammatory drugs , xii) selective serotonin reuptake inhibitors , xiii) selective serotonin and norepinephrine reuptake inhibitors, xiv) tricyclic antidepressant drugs, xv) norepinephrine modulators, xvi) lithium, xvii) valproate, and xviii) neurontin.

52. A method of treatment or prevention of pain comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

53. A method of treatment or prevention of chronic, visceral, inflammatory and/or neuropathic pain syndromes comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

54. A method of treatment or prevention of pain resulting from traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, cancer and/or chemotherapy comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

55. A method of treatment or prevention of chronic lower back pain comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

56. A method of treatment or prevention of phantom limb pain comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

57. A method of treatment or prevention of HIV- and HIV treatment-induced neuropathy, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and/or related neuralgias comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

58. A method of administering local anesthesia comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

59. A method of treatment or prevention of irritable bowel syndrome and/or Crohn's disease comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

60. A method of treatment or prevention of epilepsy and/or partial and generalized tonic seizures comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

61. A method for neuroprotection under ischaemic conditions caused by stroke or neural trauma comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

62. A method of treatment or prevention of multiple sclerosis comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

63. A method of treatment or prevention of bipolar disorder comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

64. A method of treatment or prevention of tachy-arrhythmias comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

65. A method of treatment or prevention of migraine, headache pain and/or migraine headache comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 22, or a pharmaceutically acceptable salt thereof.

ABSTRACT OF THE DISCLOSURE

Substituted triazole compounds represented by Formula I, II or III, or pharmaceutically acceptable salts thereof. Pharmaceutical compositions comprise an effective amount of the instant compounds, either alone, or in combination with one or more other therapeutically active compounds, and a pharmaceutically acceptable carrier. Methods of treating conditions associated with, or caused by, sodium channel activity, including, for example, acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain, migraine, headache pain, migraine headache, epilepsy, irritable bowel syndrome, diabetic neuropathy, multiple sclerosis, manic depression and bipolar disorder, comprise administering an effective amount of the present compounds, either alone, or in combination with one or more other therapeutically active compounds. A method of administering local anesthesia comprises administering an effective amount of a compound of the instant invention, either alone, or in combination with one or more other therapeutically active compounds, and a pharmaceutically acceptable carrier.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US04/037280

International filing date: 05 November 2004 (05.11.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/518,890
Filing date: 10 November 2003 (10.11.2003)

Date of receipt at the International Bureau: 13 December 2004 (13.12.2004)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
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